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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 : A61K 37/02, 39/00, C07K 7/06 C07K 7/10, 13/00, 15/28 C07K 7/08

A1

(11) International Publication Number: WO 91/19511

(43) International Publication Date: 26 December 1991 (26.12.91)

(21) International Application Number: PCT/US91/04338

(22) International Filing Date: 18 June 1991 (18.06.91)

(30) Priority data:

539,842	18 June 1990 (18.06.90)	US
637,830	4 January 1991 (04.01.91)	US

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(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: CONTROLLING CELLULAR IMMUNE/INFLAMMATORY RESPONSES WITH β2 INTEGRINS

(57) Abstract

The invention features human CD11 recombinant or synthetic peptide capable of inhibiting a CD11/CD18-mediated immune response, a purified DNA encoding a human CD11b peptide, soluble heterodimeric molecules composed of a CD11 peptide and a CD18 peptide, and a method of controlling any phagocyte-mediated tissue damage such as that associated with reduced perfusion of heart tissue during acute cardiac insufficiency.

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CONTROLLING CELLULAR IMMUNE/INFLAMMATORY RESPONSES WITH β2 INTEGRINS

Background of the Invention

This invention, at least in part, was funded by a grant from the United States Government and the Government has certain rights in the invention.

This application is a continuation-in-part of my earlier, co-pending application USSN 539,842, filed June 18, 1990, which is in turn a continuation-in-part of my earlier application USSN 212,573, filed June 28, 1988, now abandoned, both of which are hereby incorporated by reference.

This invention relates to controlling cellular immune/inflammatory responses, particularly phagocyte-mediated tissue injury and inflammation.

Circulating phagocytic white blood cells are an important component of the cellular acute inflammatory response. It is believed that a number of important biological functions such as chemotaxis, immune adherence (homotypic cell adhesion or aggregation), adhesion to endothelium, phagocytosis, antibody-dependent cellular cytotoxicity, superoxide, and lysosomal enzyme release are mediated by a family of leukocyte surface glycoprotein adhesion receptors known as β_2 integrins or the CD11/CD18 complex. Arnaout et al., *Blood* 75:1037 (1990). Inherited deficiency of CD11/CD18 impairs leukocyte adhesion-dependent inflammatory functions and predisposes to life-threatening bacterial infections. Dana et al., *J. Clin. Invest.* 73:153 (1983); Arnaout et al., *J. Clin. Invest.* 74:1291 (1984).

The CD11/CD18 family consists of three heterodimeric surface glycoproteins, each with a distinct

α subunit (CD11a, CD11b or CD11c) non-covalently associated with a common β subunit (CD18). The divalent cations Ca^{+2} and Mg^{2+} are essential in the stabilization and function of the αβ (CD11/CD18) complex.

The β2 integrins are expressed only on leukocytes. While CD11a/CD18 (also known as LFA-1, TA-1) is expressed on all leukocytes, CD11b/CD18 and CD11c/CD18 (also known as LeuM5 or p150,95) are expressed primarily on monocytes, polymorphonuclear leukocytes, macrophages and natural killer cells CD11c/CD18 is also expressed on certain lymphocytes. Arnaout, *Blood* 75:1037 (1990).

CD11a/CD18, and not CD11b/CD18 or CD11c/CD18, is expressed on B- and T-lymphocytes; accordingly CD11a/CD18 plays a role in mitogen-, antigen-, and alloantigen-induced proliferation, T-cell-mediated cytotoxicity, lymphocyte aggregation, and Ig production. In contrast, all three CD11/CD18 molecules are important for monocyte/macrophage and granulocyte adhesion-dependent functions.

It is believed that CD11b/CD18 and CD11c/CD18 mediate enhanced adhesiveness of activated phagocytes through quantitative and qualitative changes in these proteins on the surface of activated cells. For example, in granulocytes, these proteins are translocated from intracellular storage pools present in secondary and tertiary granules. Arnaout et al., *J. Clin. Invest.* 74:1291 (1984); Arnaout et al., *New Eng. J. Med.* 312:457 (1985); Todd et al., *J. Clin. Invest.* 74:1280 (1984).

CD11b/CD18 is also known as complement receptor type 3 (CR3), Mo1, Mac-1 or MAM. See, Arnaout et al., *J. Clin. Invest.* 72:171 (1983), and references cited therein; Dana et al., *J. Immunol.* 137:3259 (1986); Wallis

et al., *J. Immunol.* 135:2323 (1985); Arnaout et al., *New Eng. J. Med.* 312:457 (1985); Dana et al., *J. Clin. Invest.* 73:153 (1984); and Beatty et al., *J. Immunol.* 131:2913 (1983). Like all β2 integrins, CD11b/CD18 consists of two non-covalently associated subunits. Kishimoto et al., *Cell* 48:681 (1987); Law et al., *EMBO J.* 6:915 (1987); Arnaout et al. *J. Clin. Invest.* 72:171 (1983). The α subunit of CD11b/CD18 has an apparent molecular mass of 155-165 kD and associates non-covalently with a β subunit, CD18, of apparent molecular mass 95 kD. Todd et al., *Hybridoma* 1:329 (1982).

Monoclonal antibodies have been used to identify at least two distinct functional domains of CD11b/CD18, one mediating homotypic and heterotypic adhesion and the other mediating binding to the complement C3 fragment (iC3b), the major C3 opsonin *in vivo*. Dana et al., *J. Immunol.* 137:3259 (1986).

Law et al., *EMBO J.* 6:915 (1987) and Kishimoto et al., *Cell* 48:681 (1987) disclose the nucleotide sequence of human CD18. Arnaout et al., *J. Cell Biol.* 106:2153 (1988); Corbi et al., *J. Biol. Chem.* 263:12403 (1988); and Hickstein et al., *Proc. Nat'l. Acad. Sci. USA* 86:275 (1989) disclose the nucleotide sequence of human CD11b. Larson et al., *J. Cell. Biol.* 108:703 (1989) disclose the nucleotide sequence of CD11a. Corbi et al., *EMBO J.* 6:4023 (1987) disclose the nucleotide sequence of CD11c.

Cosgrove et al.(*Proc. Nat'l. Acad. Sci. USA* 83:752, 1986) report a human genomic clone which produces "a molecule(s)" reactive with monoclonal antibodies to CD11b.

Sastre et al. (*Proc. Nat'l. Acad. Sci. USA* 83:5644, 1986) report a mouse genomic clone coding for an amino-terminal partial exon of murine CD11b. Pytela et

al., *EMBO J.* 7:1371 (1988) report a cDNA sequence of murine CD11b.

Simpson et al., *J. Clin. Invest.* 81:624 (1988) disclose that a monoclonal antibody (904) directed to an adhesion-promoting domain of CD11b (Dana et al., *J. Immunol.* 137:3259, 1986) reduces the extent of cardiac damage in dogs associated with myocardial infarction, presumably by limiting reperfusion injury. Vedder et al. (*J. Clin. Invest.* 81:939, 1988) similarly found that a monoclonal antibody directed against CD18 subunit of CD11b/CD18 reduced organ injury and improved survival from hemorrhagic shock in rabbits. In animal models, anti-CD11/CD18 antibodies have been shown to have protective effects in shock, frostbite, burns, cerebral edema, onset of diabetes mellitus (Hutchings et al., *Nature* 348:639, 1990) and transplant rejection. Reviewed in Carlos et al., *Immunol. Rev.* 114:5 (1990).

Summary of the Invention

The peptides and heterodimeric proteins of the invention are capable of antagonizing CD11/CD18 (β2 integrin) mediated immune response. CD11/CD18 mediated immune responses which it may be desirable to block include acute inflammatory functions mediated by neutrophils. The molecules of the invention are useful for treatment of ischemia reperfusion injury (e.g., in the heart, brain, skin, liver or gastrointestinal tract), burns, frostbite, acute arthritis, asthema, and adult respiratory distress syndrome. Peptides and heterodimeric proteins of the invention may also be useful for blocking intra-islet infiltration of macrophages associated with insulin-dependent diabetes mellitus.

The invention features a purified peptide which includes at least one extracellular region of a β2 integrin subunit capable of inhibiting a CD11/CD18 mediated immune response, the peptide lacks the transmembrane and cytoplasmic portions of the β2 integrin subunit. In a preferred embodiment the β2 integrin subunit is a human β2 integrin subunit; more preferably the β2 integrin subunit is CD11a, CD11b, CD11c or CD18; most preferably the β2 integrin subunit is CD11b. Preferably, the peptide includes all or part of the A domain of CD11b. More preferably the peptide includes one of the following sequences: DIAFLIDGS (SEQ ID NO: 32); FRRMKEFVS (SEQ ID NO: 33); FKILVVITDGE (SEQ ID NO: 34); VIRYVIGVGDA (SEQ ID NO: 35); DGEKFGDPLG (SEQ ID NO: 36); YEDVIPEADR (SEQ ID NO: 37); DGEKFGDPLGYEDVIPEADR (SEQ ID NO: 17); NAFKILVVITDGEKFGDPLGYEDVIPEADREGV (SEQ ID NO: 50); DGEKF (SEQ ID NO: 51). In preferred embodiments, the peptide includes the amino acid sequence YYEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 38); the peptide includes the amino acid sequence KSTRDRLR (SEQ ID NO: 15). Preferably, the peptide includes one of the following amino acid sequences:

AYFGASLCSVDVDSNGSTDLVLIGAP (SEQ ID NO: 1);
GRFGAALTVLGDVNGDKLTDVAIGAP (SEQ ID NO: 2);
QYFGQSLSGGQDLTMDGLVDLTVGAQ (SEQ ID NO: 3);
YEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 4);
DIAFLIDGSGSIIPHDFRRMK (SEQ ID NO: 5);
RRMKEFVSTVMEQLKKSKTLF (SEQ ID NO: 6);
SLMQYSEEFRIHFTFKEFQNN (SEQ ID NO: 7);
PNPRSLVKPITQLLGRTHTATGIRK (SEQ ID NO: 8);
RKVVRELFNITNGARKNAFK (SEQ ID NO: 9);
FKILVVITDGEKFGDPLGYEDVIPEADR (SEQ ID NO: 10);
REGVIRYVIGVGDAFRSEKSR (SEQ ID NO: 11);

QELNTIASKPPRDHVFQVNNFE (SEQ ID NO: 12); ALKTIQNQLREKIFAIEGT (SEQ ID NO: 13); QTGSSSSFEHEMSQE (SEQ ID NO: 14); FRSEKSRQELNTIASKPPRDHV (SEQ ID NO: 16); KEFQNNPNPRSL (SEQ ID NO: 18); GTQTGSSSSFEHEMSQEG (SEQ ID NO: 19); SNLRQQPQKFPEALRGCPQEDSD (SEQ ID NO: 20); RQNTGMWESNANVKGT (SEQ ID NO: 21); TSGSGISPSHSQRIA (SEQ ID NO: 22); NQRGSLYQCDYSTGSCEPIR (SEQ ID NO: 23); PRGRARWQC (SEQ ID NO: 24); KLSPRLQYFGQSLSGGQDLT (SEQ ID NO: 25); QKSTRDRLREGQ (SEQ ID NO: 26); SGRPHSRAVFNETKNSTRRQTQ (SEQ ID NO: 27); CETLKLQLPNCIEDPV (SEQ ID NO: 28); FEKNCGNDNICQDDL (SEQ ID NO: 29); VRNDGEDSYRTQ (SEQ ID NO: 30); SYRKVSTLQNQRSQRS (SEQ ID NO: 31).

Preferably, the peptide includes one or more metal binding domains of CD11b. More preferably, the metal binding domains encompass amino acids 358-412, 426-483, 487-553, and 554-614 of CD11b. Most preferably, the peptide includes one of the following sequences: DVDSNGSTD (SEQ ID NO: 46); DVNGDKLTD (SEQ ID NO: 47); DLTMDGLVD (SEQ ID NO: 48); DSDMNDAYL (SEQ ID NO: 49).

In a preferred embodiment, the peptides are soluble under physiological conditions.

In a related aspect, the invention features a heterodimer which includes a first peptide and a second peptide; the first peptide includes at least one extracellular region of a CD11 subunit and lacks the transmembrane and cytoplasmic portions of the CD11 subunit; the second peptide comprising at least one extracellular region of a CD18 subunit and lacks the transmembrane and cytoplasmic portions of the CD18 subunit; the first and second peptides are associated to form the heterodimer; and the heterodimer is capable of inhibiting a CD11/CD18 mediated immune response. In preferred embodiments, the CD11 subunit is: CD11a; CD11b;

CD11c. In a more preferred embodiment, the heterodimer is $CD11b^{1089}/CD18^{699}$.

In another aspect, the invention features a method of controlling phagocyte-mediated tissue damage to a human patient. The method includes administering a therapeutic composition to a patient; the therapeutic composition includes a physiologically acceptable carrier and a peptide or a heterodimer of the invention. More preferably, the method is used to control phagocyte-mediated tissue damage due to ischemia-reperfussion. Most preferably, the method is used to control phagocyte-mediated tissue damage to the heart muscle associated with reduced perfusion of heart tissue during acute cardiac insufficiency.

In another aspect, the invention features a method of producing a recombinant β2 integrin heterodimer. The method includes the steps of: (a) providing a recombinant cell encoding a CD11 peptide lacking both the transmembrane domain and the cytoplasmic domain and a CD18 peptide lacking both the transmembrane domain and the cytoplasmic domain; (b) culturing the recombinant cell; and (c) isolating the heterodimer from the culture supernatant. More preferably, the method is used to produce a soluble recombinant β2 integrin heterodimer. In preferred embodiments, the CD11 peptide of the heterodimer is a CD11a peptide; is a CD11b peptide; is a CD11c peptide.

In another aspect, the invention features a monoclonal antibody which is raised to a peptide or a heterodimer of the invention and which is capable of inhibiting a CD11/CD18 mediated immune response.

In another aspect, the features a human CD11b recombinant peptide.

"β2 integrins" include all leukocyte adhesion molecules which include a CD18 subunit. By the "A domain of CD11b" is meant the amino acid sequence corresponding to the sequence of CD11b from Cys^{128} to Glu^{321} or an amino acid sequence produced by introducing one or more conservative amino acid substitutions in an amino acid sequence corresponding to the sequence of CD11b from Cys^{128} to Glu^{321}. "CD11/CD18-mediated immune response" includes those CD11/CD18-related functions mentioned above: chemotaxis, immune adherence (homotypic cell adhesion or aggregation), adhesion to endothelium, phagocytosis, antibody-dependent or -independent cellular cytotoxicity, and superoxide and lysosomal enzyme release. Inhibition of these immune functions can be determined by one or more of the following inhibition assays as described in greater detail below: iC3b binding, cell-cell aggregation, phagocytosis, adhesion to endothelium, and chemotaxis. As used herein, a human CD11b recombinant peptide is a chain of amino acids derived from recombinant CD11b-encoding cDNA, or the corresponding synthetic DNA. "$CD11^{1089}/CD^{18699}$" is a heterodimer which comprises amino acids 1-1089 of human CD11 and amino acids 1-699 of CD18.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

The drawings will first briefly be described.

Drawings

Figure 1 is the cDNA sequence and deduced amino acid sequence of the open reading frame of human CD11b from Arnaout et al., *J. Cell. Biol.* 106:2153 (1988).

Figure 2 is a representation of the results of an immunoprecipitation assay.

Figure 3 is a representation of the results of an immunoprecipitation assay.

Figure 4 is a representation of the results of an immunoprecipitation assay.

Figure 5 is a graph of the effect of various proteins and antibodies on neutrophil adhesion to endothelium.

Figure 6 is the cDNA sequence and deduced amino acid sequence of human CD11a from Larson et al., *J. Cell. Biol.* 108:703 (1989).

Figure 7 is the cDNA sequence and deduced amino acid sequence of human CD11c from Corbi et al., *EMBO J.* 6:4023 (1987).

Figure 8 is the cDNA sequence of human CD18 from Law et al., *EMBO J.* 6:915 (1987).

Peptides

As described in greater detail elsewhere, each member of the β2 integrin family is a heterodimer consisting of two subunits: a CD11 subunit (with at least three variants designated CD11a, CD11b, and CD11c) and a CD18 subunit. Each subunit includes a transmembrane anchor which connects a cytoplasmic segment to an extracellular segment. The two subunits interact to form a functional heterodimer. As described in greater detail below, the extracellular segments of the β2 integrin

subunits contain various functional domains which are the focus of the invention.

Without wishing to bind myself to a particular theory, it appears that the peptides of the invention antagonize CD11/CD18-mediated immune responses by competitively inhibiting binding of leukocytes bearing a member of the β_2 integrin family to the respective binding partners of that family. Specifically, the peptides of the invention include an immune-response inhibiting extracellular segment of any one of the $\beta 2$ integrin subunits --CD11a, CD11b, CD11c, CD18-- or a heterodimer composed of a portion of an α (CD11a, CD11b, or CD11c) subunit together with a portion of a β subunit (CD18). Candidate $\beta 2$ integrin subunits can be evaluated for their ability to antagonize CD11/CD18-mediated immune responses by any of several techniques. For example, subunits may be tested for their ability to interfere with neutrophil adhesion to endothelial cells using an assay described in detail below. Specific regions of the $\beta 2$ integrin subunits can be evaluated in a similar manner. Any extracellular region of a $\beta 2$ integrin subunit may be screened for its ability to interfere with CD11/CD18 mediated immune response. Regions of CD11 whose sequences are conserved between two or more subunits are preferred candidates for antagonizing CD11/CD18 - mediated immune response. For example, the A domain (corresponding to Cys^{128} to Glu^{321} of CD11b) is conserved between CD11a, CD11b, and CD11c. The A domain is 64% identical in CD11b and CD11c and 36% homologous between these two subunits and CD11a. This domain is also homologous to a conserved domain in other proteins involved in adhesive interactions including von Willebrand's factor, cartilage matrix protein, VLA2, and

the complement C3b/C4b - binding proteins C2 and factor B. The extracellular portions of CD11a, CD11b and CD11c include seven homologous tandem repeats of approximately 60 amino acids. These repeats are also conserved in the α subunits of other integrin subfamilies (e.g., fibronectin receptor). Arnaout et al., *Blood* 75:1037 (1990).

Regions of CD18 which are conserved among β intergrin subunits (i.e., the β subunits of β1, β2 and β3 integrins) are also good candidates for regions capable of interfering with CD11/CD18 - mediated immune response. For example, CD18 has four tandem repeats of an eight-cysteine motif. This cysteine-rich region is conserved among β subunits. Just amino terminal to this cysteine rich region is another conserved region, 247 amino acids long, which is conserved in several integrin β subunits.

Described in detail below are techniques for generating CD11b peptides and heterodimers. The same techniques may be used to generate CD11a, CD11c, and CD18 peptides as well as CD11a/CD18 and CD11c/CD18 heterodimers. Fig. 6 depicts the cDNA sequence of human CD11a (SEQ ID NO: 39); Fig. 7 depicts the cDNA sequence of human CD11c (SEQ ID NO:); Fig. 8 depicts the cDNA sequence of CD18 (SEQ ID NO: 41).

DNA molecules encoding all or part of CD11a, CD11b, CD11c or CD18 can be obtained by means of polymerase chain reaction amplification. In this technique two short DNA primers are used to generate multiple copies of a DNA fragment of interest from cells known to harbor the mRNA of produced by the gene of interest. This technique is described in detail by Frohman et al., *Proc. Nat'l Acad Sci. USA* 85:8998 (1988). Polymerase chain reaction methods are generally described

by Mullis et al. (U.S. Patent Nos. 4,683,195 and 4,683,202).

For example, to clone a portion of CD11a, the known sequence of CD11a is used to design two DNA primers which will hybridize to opposite strands outside (or just within) the region of interest. The primers must be oriented so that when they are extended by DNA polymerase, extension proceeds into the region of interest. To generate the CD11a DNA, poyA RNA is isolated from cells expressing CD11a. A first primer and reverse transcriptase are used to generate a cDNA form the mRNA. A seond primer is added; and *Taq* DNA polymerase is used to amplify the cDNA genrated in the previous step. Alternatively, the known sequences of CD11a, CD11b, CD11c and CD18 can be used to design highly specific probes for identifying cDNA clones harboring the DNA of interest. A cDNA library suitable for isolation of CD11a, CD11b, and CD11c DNA can be generated using phorbol ester-induced HL-60 cells (ATCC Accession No. CCL 240) as described by Corbi et al. (*EMBO J.* 6:4023, 1987) and Arnaout et al., *Proc. Nat'l Acad Sci. USA* 85:2776, 1988); CD18 DNA can be isolated from a library generated using U937 cells (ATCC Accession No. CRL 1593) as described by Law et al. (*EMBO J.* 6:915, 1987). These cell lines are also suitable for generating cDNA by polymerase chain reaction amplification of mRNA as sescribed above.

Heterodimers comprised of part of CD11c and CD18 can be produced as described below for CD11b/CD18 by changing a codon amino terminal to the transmembrane region (e.g. Pro^{1086}) to a stop codon. Heterodimers comprised of part of CD11a can be produced by changing a codon amino terminal to the transmembrane region (e.g.,

Lys^{1087}) to a stop codon. DNA encoding the truncated CD11 subunit is then introduced into cells along with DNA encoding a similarly truncated CD18 molecule (described below). These cells are then used as a source of heterodimer.

Isolation of a Human CD11b cDNA clone.

A 378 base pair (bp) cDNA clone encoding guinea pig CD11b was used as a probe to isolate three additional cDNA clones from a human monocyte/lymphocyte cDNA library as described in Arnaout et al., *Proc. Nat'l. Acad. Sci. USA* 85:2776 (1988); together these three clones contain the 3,048 nucleotide sequence encoding the CD11b gene shown in Fig. 1 (SEQ ID NO: 40). Arnaout et al., *J. Cell. Biol.* 106:2153 (1988).

In order to express CD11b, a mammalian expression vector was constructed by assembling the above-described three cDNA clones. Appropriate restriction enzyme sites within the CD11b gene can be chosen to assemble the cDNA inserts so that they are in the same translation reading frame. Arnaout et al., *J. Clin. Invest.* 85:977 (1990). A suitable basic expression vector can be used as a vehicle for the 3,048 bp complete cDNA fragment encoding the human CD11b peptide; the recombinant cDNA can be expressed by transfection into, e.g., COS-1 cells, according to conventional techniques, e.g., the techniques generally described by Aruffo et al., *Proc. Nat'l. Acad. Sci. USA* 84:8573 (1987) or expressed in *E. coli* using standard techniques. Smith et al., *Gene* 67:31 (1988).

Isolation of CD11b Peptide from Mammalian Cells

The CD11b protein can be purified from the lysate of transfected COS-1 cells, using affinity chromatography and lentil-lectin Sepharose and available anti-CD11b

monoclonal antibody as described by Pierce et al. (1986) *supra* and Arnaout et al., *Meth. Enzymol.* 150:602 (1987).

If the desired CD11b peptide is shorter than the entire protein, DNA encoding the desired peptide can be expressed in the same mammalian expression vector described above using the selected DNA fragment and the appropriate restriction enzyme site, as outlined above. The selected DNA fragment may be isolated according to conventional techniques from one of the CD11b cDNA clones or may be synthesized by standard polymerase chain reaction amplification, as described above. See also Saiki et al., (*Science* 239:487, 1988).

Characterization of the CD11b Polypeptide

The coding sequence of the complete CD11b protein is preceded by a single translation initiation methionine. The translation product of the single open reading frame begins with a 16-amino acid hydrophobic peptide representing a leader sequence, followed by the NH_2-terminal phenylalanine residue. The translation product also contained all eight tryptic peptides isolated from the purified antigen, the amino-terminal peptide, and an amino acid hydrophobic domain representing a potential transmembrane region, and a short 19-amino acid carboxy-terminal cytoplasmic domain (Fig. 1 illustrates the amino acid sequence of CD11b; SEQ ID NO: 43). The coding region of the 155-165 kD CD11b (1,136 amino acids) is eight amino acids shorter than the 130-150 kD alpha subunit of CD11c/CD18 (1,144 amino acids). The cytoplasmic region of CD11b contains one serine residue that could serve as a potential phosphorylation site. The cytoplasmic region is also relatively rich in acidic residues and in proline (Fig.

1). Since CD11b/CD18 is involved in the process of phagocytosis and is also targeted to intracellular storage pools, these residues are candidates for mediating these functions. The long extracytoplasmic amino-terminal region contains three or four metal-binding domains (outlined by broken lines in Fig. 1) that are similar to Ca^{2+}-binding sites found in other integrins. Each metal binding site may be composed of two noncontiguous peptide segments and may be found in the four internal tandem repeats formed by amino acid residues 358-412, 426-483, 487-553, and 554-614. The portion of the extracytoplasmic domain between Tyr^{465} and Val^{492} is homologous to the fibronectin-like collagen binding domain and IL-2-receptor. The extracytoplasmic region also contains an additional unique 187-200 amino acid domain, the A domain, between Cys^{128} to Glu^{321}, which is not present in the homologous (α) subunits of fibronectin, vitronectin, or platelet IIb/IIIa receptors. This sequence is present in the highly homologous CD11c protein (α of p150,95) with 64% of the amino acids identical and 34% representing conserved substitutions. Arnaout et al., *J. Cell Biol.* 106:2153, 1988; Arnaout et al. *Blood* 75:1037 (1990). It is known that both CD11b/CD18 and CD11c/CD18 have a binding site for complement fragment C3 and this unique region may be involved in C3 binding. This region of CD11b also has significant homology (17.1% identity and 52.9% conserved substitutions) to the collagen/heparin/platelet GpI binding regions of the mature von Willebrand factor (domains A1-A3). The A domain is also homologous to a region in CD11a. Larson et al., *J. Cell Biol.* 108:703 (1989). The A domain is also referred to as the L domain or the I domain. Larson et al., *supra* (1988); Corbi et

al., *J. Biol. Chem.* 263:12,403 (1988).

CD11b Peptides

The following peptides can be used to inhibit CD11b/CD18 activity: a) peptides identical to the above-described A domain of CD11b, or a portion thereof, e.g., DIAFLIDGS (SEQ ID NO:32), FRRMKEFVS (SEQ ID NO:33), FKILVVITDGE (SEQ ID NO:34), DGEKFGDPLGYEDVIPEADR (SEQ ID NO:17), or VIRYVIGVGDA SEQ ID NO:35); b) peptides identical to the above-described fibronectin-like collagen binding domain, or a portion thereof, e.g., YYEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO:38); c) peptides identical to one or more of the four metal binding regions of CD11b, or a portion thereof, e.g., DVDSNGSTD (SEQ ID NO:46), DVNGDKLTD (SEQ ID NO:47), DLTMDGLVD (SEQ ID NO:48), DSDMNDAYL (SEQ ID NO:49); d) peptides substantially identical to the complete CD11b; or e) other CD11b domains, e.g. KSTRDRLR (SEQ ID NO:15).

Also of interest is a recombinant peptide which includes part of the A domain, e.g, NAFKILVVITDGEKFGDPLGYEDVIPEADREGV (SEQ ID NO: 50). The A domain binds iC3b, gelatin, and fibrinogen and binding is disrupted by EDTA. The A domain also binds both Ca^{2+} and Mg^{2+}. This result unexpected since the A doamin lies outside of the region of CD11b previously predicted (Arnaout et al., *J. Cell Biol.* 106:2153, 1988; Corbi et al., *J. Biol. Chem.* 25:12403, 1988) to contain metal binding sites.

Heterodimers

It is advantageous to administer the heterodimer formed by the CD11b and CD18 proteins. Expression of CD11b is described elsewhere in this application. Expression of CD18 has been reported by others. Law et al. *Embo, J.* 6:915 (1987); Kishimoto et al. *Cell* 48:681

(1987). The strategies described above or in those reports can be used to obtain CD18 to make such a heterodimer. Preferred heterodimers are soluble under physiological conditions. The heterodimer described below is generated by changing the codon for Leu^{1090} in CD11b (SEQ ID NO: 40) to a stop codon and the codon for Asn^{700} of CD18 (SEQ ID NO: 41) to a stop codon. Other potentially soluble heterodimers can be generated by introducing a stop codon at positions amino terminal to those described below.

Generation of Soluble Heterodimers

A soluble form of a CD11b/CD18 heterodimer was produced in COS cells. To produce this molecule the codons for Leu^{1090} and Asn^{700} located at the predicted extracellular boundaries of CD11b and CD18 respectively, were replaced with in-frame translational stop codons using oligonucleotide-directed gapped-duplex mutagenesis of the wild-type cDNAs (described below).

To determine if COS cells can express a soluble form of CD11b/CD18, COS cells were co-transfected with cDNA encoding the truncated forms of CD11b ($CD11b^{1089}$) and CD18 ($CD11^{699}$). Secreted proteins were analyzed by immunoprecipitation and SDS-PAGE. The results of this analysis are presented in Fig. 2.

Briefly, COS cells were transfected as previously described (Arnaout et al., *J. Clin. Invest.* 85:977, 1990). 7×10^6 transfected cells were labeled overnight with 0.1 mCi of ^{35}S methionine, and the harvested supernatants were used for immunoprecipitation with NS1, a non-reactive monoclonal antibody (mAb) (lane 1); 44a, an anti-CD11b mAb (lane 2); or TS18, an anti-CD18 mAb (lane 3). Immunoprecipitation and antibodies as described by Arnaout et al., *J. Cell. Physiol.* 137:305

(1988); Trowbridge et al., *J. Exp. Med.* 154:1517 (1981); and Sanchez-Madrid et al., *J. Exp. Med.* 158:1785 (1983).

As shown in Fig. 2, both $CD11b^{1089}$ and $CD18^{699}$ were immunoprecipitated from supernatants of cells transfected with DNA encoding the truncated subunits. The secreted $CD11b^{1089}$ had an apparent molecular weight of 149 kD; the secreted $CD18^{699}$ had an apparent molecular weight of 84 kD (compared to 155 kD and 94 kD respectively for the wild-type subunits). Arnaout et al., *New Engl. J. Med.* 312:457 (1985); Dierner et al., *J. Immunol.* 135:537 (1985); Arnaout et al., *J. Clin. Invest.* 72:171 (1983); Klebanoff et al., *J. Immunol.* 134:1153 (1985). That mAbs directed against either the CD11b or CD18 immunoprecipitated both truncated forms, indicates that the secreted subunits are expressed as an $CD11b^{1089}/CD18^{699}$ complex and that neither the cytoplasmic nor the transmembrane region of the subunits are necessary for heterodimer formation. These mAbs did not precipitate receptor subunits from the supernatants of mock-transfected cells. Arrowheads at left indicate the positions of molecular weight size markers: myosin (200kD), phosphorylase b (92.5 kD), bovine serum albumin (69 kD), and ovalbumin (46 kD). Arrows at right indicate the expected positions of $CD11b^{1089}$ and $CD18^{699}$.

$CD11b^{1089}/CD18^{699}$ was next tested for its ability to bind iC3b (the receptor bound by wild-type CD11b/CD18). Briefly, COS cells were transfected $CD11b^{1089}$ and $CD18^{699}$ cDNA as described above. Cells were labeled with ^{35}S-methionine as described by Dana et al., *J. Clin. Invest.* 79:1010 (1987). Supernatants from both co-transfected COS cells (7×10^6 cells) and mock-transfected COS cells (7×10^6 cells) were concentrated to one ml using collodion bags (10,000 MW cut off). 100

μl of the concentrated supernatant were used for immunoprecipitation, and the rest of the supernatant was incubated with C3b-sepharose or iC3b-sepharose. C3b-sepharose and iC3b-sepharose was washed, eluted with 0.4 M NaCl and the eluted proteins were analyzed by SDS-PAGE and autoradiography. Binding of wild-type, membrane-bound CD11b/CD18 to iC3b-sepharose or C3b-sepharose was performed as described by Arnaout et al., (*In Methods in Enzymology*, DiSabato, Ed., Acad. Press Inc., Fl., 1987) using the detergent soluble fraction from 1 x 10^8 ^{125}I-surface-labelled neutrophils.

Fig. 3 illustrates the results of SDS-PAGE analysis of neutrophil-derived ^{125}I-surface-labeled glycoproteins eluted from C3b-sepharose and iC3b-sepharose. Eluants from C3b-sepharose (lane a) contained complement receptor type 1 (250kD) and the C3-binding regulatory protein gp45/70 (45-70 kD). Eluants from iC3b-sepharose (lane b) contained two additional proteins at 155 kD, 94 kD, representing wild-type CD11b and CD18. CD11b/CD18 was immunoprecipitated with 44a mAb (an anti-CD11b mAb) from material eluted from iC3b-sepharose (lane d), but not from material eluted from C3b-sepharose (lane c), confirming previous results. Malhorta et al., *Eur. J. Immunol.* 16:177, (1986). The arrowheads at right indicate the positions of molecular weight standards: myosin (200 kD), phosphorylase b (92.5 kD), and bovine serum albumin (69 kD). The arrows at left indicate the expected position of CR1, CD11b, CD18 and gp45/70.

Fig. 4 shows the results of SDS-PAGE analysis of CD11b^{1089}/CD18^{699} heterodimer binding to iC3b. An anti-CD11b mAb (44a) was used to immunoprecipitate proteins from culture supernatants of mock-transfected COS cells (lane a), and from COS cells co-transfected with CD11b^{1089}

and $CD18^{699}$ cDNAs (lane b). No specific radiolabeled material was present in eluant of iC3b-sepharose exposed to culture supernatant of mock-transfected COS cells (lane c). $CD11b^{1089}/CD18^{699}$ was eluted from iC3b-sepharose (lane d), but not from C3b-sepharose (lane e) exposed to culture supernatant of co-transfected cells. Arrowheads at right indicate the positions of molecular weight standard standards (as in Fig. 2). Arrows at left indicate the expected positions of $CD11b^{1089}$ and $CD18^{699}$. Similar results were seen with supernatants from two other transfections.

The ability of $CD11b^{1089}/CD18^{699}$ to inhibit binding of human neutrophils to inflamed endothelium was examined and compared to the inhibition induced by anti-CD11b mAb and anti-CD18 mAb. Adherence of purified human neutrophils to confluent monolayers of human umbilical vein endothelial cells (HUVE) pre-treated with recombinant IL-1 (10 units/ml for 4 hours at 37°C) was measured as described by Arnaout et al.,(*J. Cell. Physiol.* 137:305, 1988) with the following modifications. Neutrophils were labeled with carboxyfluorescein (CF, Molecular Probes, Eugene, OR) by incubating 4×10^6 cells with 30 μg of CF in one ml of Tris-buffered saline for 10 minutes on ice, followed by three washes. HUVE were pre-incubated for 10 minutes at 37°C with supernatants of COS cells co-transfected with $CD11b^{1089}$ and $CD18^{699}$ cDNA supernatants, or for 5 minutes at room temperature with the non-reactive monoclonal antibody NS1, 44a (anti-CD11b) or TS18 (anti-CD18) ascites (1:100 dilution). Labeled neutrophils were then added and incubation was continued for an additional 10 minutes. The plates HUVE were washed twice, and adherent neutrophils were harvested by washing with 0.1% SDS and 0.1N NaOH.

Relative numbers of neutrophils were measured (at Exc., 490 nm; Em, 300nm) using a Fluorometer (SLM 8000, SLM Aminco, Urbana, IL). All assays were done in triplicate. Labels along the horizontal axis indicate the molecule added to HUVE. 'Buffer' indicates that no antibodies were added. 'Sham' indicates that supernatant from mock transfected cells was added.

As shown in Fig. 5, culture supernatants containing $CD11b^{1089}/CD18^{699}$ (approximately 10-50 ng/ml) were found to be at least as effective in blocking neutrophil adhesion to rIL-1-induced endothelium as monoclonal antibodies directed against CD11b or CD18. $CD11b^{1089}/CD18^{699}$ was more effective than 44a mAb (an anti-CD11b mAb) in inhibiting adhesion to rIL-1-activated endothelium and comparable to inhibition seen using TS18 mAb (an anti-CD18 mAb), suggesting the presence of multiple functional sites on $CD11b^{1089}$ and/or the possibility that CD18 (like other β integrins) contains a recognition site(s) for interacting with ligand(s) expressed on endothelium.

Generation of Truncated CD11b and CD18 PAT-X plasmid containing the partial CD18 cDNA clone J19 (Law et al. *supra*, 1987) was linearized with HindIII or digested with NcoI (to generate a 1331 bp gap). These two plasmids were mixed with an excess of the synthetic and 5'-end phosphorylated 18-mer (5'-aggccccTaGatcgccgc) containing desired nucleotide mutations (caps). The mixture was denatured by boiling and renatured by stepwise cooling. Reannealed DNA (containing single-stranded region to which the mutant 18-mer is hybridized) was primer extended to fill the gap, and used to transform *E. coli* strain BMH 71-18 mutL. Arnaout et al., *J. Clin. Invest.* 85:977 (1990). Plasmids containing the mutation were

identified by differential hybridization with ^{32}P-labeled wild-type- or mutant 18-mers and DNA used to transform *E. coli* JM109. Positive colonies were identified following rehybridization, sequenced to verify the mutation, then used to replace the corresponding fragment in wild-type full length CD18 cDNA cloned in πH3M expression vector. Arnaout et al., *J. Clin. Invest.* 85:977 (1990). A stop codon was similarly introduced in CD11b. Blue Script (Stratagene, La Jolla, CA) plasmid vector containing the full coding region of membrane-bound CD11b was used. A mixture of KpnI-linearized and gapped (by removing a SmaI fragment, 1048 bp long) CD11b cDNAs were mixed with an excess of the synthetic mutant 18-mer (5'-caaccccTAgccgctcat). Mutant plasmid was produced and isolated as detailed above.

Monoclonal Antibodies

Monoclonal antibodies directed against CD11 or CD18 can be used to antagonize CD11/CD18-mediated immune response. Useful monoclonal antibodies can be generated by using a peptide of the invention as an immunogen. For example, monoclonal antibodies can be raised against the A domain of CD11b, CD11a or CD11c.

Anti-CD11b monoclonal antibodies which inhibit iC3b binding (mAb 903), neutrophil adhesive interactions, e.g., aggregation and chemotaxis, (mAb 904), or both activities (mAb44a) have been identified. Other monoclonal antibodies (OKM-1, which inhibits fibrinogen binding, and OKM9) have also been mapped to this region. Dana et al., *J. Immunol.* 137:3259 (1986). These monoclonal antibodies recognize epitopes in the A domain of CD11b. Dana et al., *JASON* 1:549 (1990).

Additional useful monoclonal antibodies can be generated by standard techniques. Preferably, human

monoclonal antibodies can be produced. Human monoclonal antibodies can be isolated from a combinatorial library produced by the method of Huse et al. (*Science*, 246:1275, 1988). The library can be generated *in vivo* by immunizing nude or SCID mice whose immune system has been reconstituted with human peripheral blood lymphocytes or spleen cells or *in vitro* by immunizing human peripheral blood lymphocytes or spleen cells. The immunogen can be any CD11b or CD18 peptide. Similar techniques are described by Duchosal et al., J. Exp. Med. 92:985 (1990) and Mullinax et al., Proc. Nat'l. Acad. USA 87:8095 (1990).

Peptides derived from the A domain of CD11a, CD11b, or CD11c are preferred immunogens. These peptides can be produced in *E. coli* transformed by a plasmid encoding all or part of the A domain.

A CD18 peptide can also be used as an immunogen. Three anti-CD18 mAbs with anti-inflammatory properties (TS18, 10F12, 60.3) have been identified. Binding each of these antibodies to CD18 can be abrogated by a specific point mutation within a particular region of CD18 (Asp^{128} to Asn^{361} of Fig. 8) (SEQ ID No.: 45). Peptide corresponding to this region can be produced in *E. coli* using a plasmid encoding the A domain.

<u>Assays for CD11b (or CD11c) peptides, heterodimers and monoclonal antibodies</u>

CD11b (or CD11c) peptides, heterodimers, and monoclonal antibodies such as those described above, can be tested *in vitro* for inhibition in one of the following five assays: iC3b binding, inhibition of phagocytosis, inhibition of monocyte/granulocyte adhesion to enclothelium, inhibition of chemotaxis, or inhibition of cell-cell aggregation. Alternatively, they may be tested

in vivo for controlling damage associated with reduced perfusion or immune injury of tissues, as a result of myocardial infarction, burns, frost bite, glomerulonephritis, asthma, adult respiratory distress syndrome, transplant rejection, onset of diabetes mellitus, ischemia, colitis, shock liver syndrome, and resuscitation from hemorrhagic shock.

Inhibition of Granulocyte or Phagocyte Adhesion to iC3b-Coated Erythrocytes or Bacteria

The antimicrobial activity of the neutrophil depends to a significant degree on the ability of this cell to establish a firm attachment to its target. For this purpose, neutrophils possess a number of specific cell surface receptors that promote this interaction, such as a receptor which binds to complement C3 (iC3b), e.g. the CD11b/CD18 receptor. Human neutrophilic polymorphonuclear granulocytes can be isolated from EDTA-anticoagulated blood on Ficoll-Hypaque gradients. Boyum, *Scand. J. Clin. Invest.* (Suppl.) 21:77 (1968) modified as described by Dana et al., *J. Clin. Invest.* 73:153 (1984). Phagocytes can be prepared by incubating the mononuclear cell fraction (obtained from Ficoll-Hypaque centrifugation) on plastic petri dishes. Todd et al., *J. Immunol.* 126:1435 (1981). Peptides of the invention can be tested for their ability to inhibit iC3b mediated binding of granulocytes to sheep erythrocytes as described in Dana et al. *supra*, 1984; and Arnaout et al., *supra*, 1985.

Inhibition of Phagocytosis

Phagocytosis is an important biological function resulting in clearing of damaged tissue from the body, and in elimination of foreign particles (bacteria, fungi). An *in vitro* test for inhibition of phagocytosis

is described in Arnaout et al., *New Eng. J. Med.* 306:693 (1982).

Inhibition Adhesion to Endothelium.

Granulocytes/monocytes must cross vascular endothelium during their egress from blood to extravascular tissues. Studies of leukocyte kinetics in animals indicate that acute inflammatory reactions may be marked by a massive increase in transendothelial monocyte/granulocyte traffic. In many chronic inflammatory lesions, perivascular monocytes accumulate in skin windows more slowly than neutrophils, but later become the predominant cell type. In addition, monocytes leaving the circulation can rapidly acquire the morphology of resident tissue macrophages--in some cases within a few hours of their departure from plasma. Thus, vascular endothelium may be considered an important substrate with which monocytes/granulocytes must interact during adherence, diapedesis, and differentiation. An *in vitro* assay for monocyte/granulocyte interaction with the vessel wall consists of binding radiolabeled or fluorescein monocyte/granulocyte preparations to cultured vascular endothelium, as described in Arnaout et al., *J. Cell Physiol.* 137:305 (1988). Mentzer et al., *J. Cell Physiol.* 125:285 (1986) describes a lymphocyte adhesion assay. These endothelial adhesion assays are appropriate for CD11a, CD11b or CD11c peptides, heterodimers and monoclonal antibodies when the endothelial cells are pre-activated. When the granulocytes/monocytes (or leukocytes) are pre-activated, these assays are suitable for CD11b peptides, heterodimers or monoclonal antibodies.

Inhibition of Chemotaxis.

The ability of cells of the immune system to

migrate is essential to the cellular immune response that results in tissue inflammation. Therefore, a peptide of the invention can be tested for its ability to inhibit chemotaxis, as described in Dana et al., (1986), *supra*.

Cell-Cell Aggregation

A granulocyte aggregation assay can be performed as described by. Arnaout et al., *New Engl. J. Med.* 306:693 (1982). Aggregation can be induced by zymosan-activated autologous serum or with chemotactic peptides, e.g. FMLP. Aggregation can then be recorded as incremental change in light transmission [ΔT] using a platelet aggregometer. The results can be confirmed by phase microscopy.

Assays for CD11a peptides, heterodimers and monoclonal antibodies

CD11a peptides, heterodimers and monoclonal antibodies can be tested using the inhibition of endothelial adhesion assay (described above) or a lymphocyte proliferation assay. Arnaout et al., *J. Clin. Invest.* 74:1291 (1984) describes an assay for inhibition of antigen/mitogen induced lymphocyte proliferation.

In Vivo Model for Testing Peptide

Damage to tissues injured by ischemia-reperfussion (e.g., heart tissue during myocardial infarction) can be minimized by administering to an animal an inhibitor of CD11/CD18 mediated immune response. A peptide of the invention may be tested for *in vivo* effectiveness using animals, e.g., dogs, which have been induced to undergo myocardial infarction. See, e.g. Simpson et al. *supra*.

Use

The peptide or monoclonal antibody can be administered intravenously in saline solution generally

on the order of mg quantities per 10 kilograms of body weight. The peptide can be administered in combination with other drugs, for example, in combination with, or within six hours to three days after a clot dissolving agent, e.g., tissue plasminogen activator (TPA), Activase, or Streptokinase.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

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(ii) TITLE OF INVENTION: Controlling Cellular Immune/Inflamatory Responses with B2 Integrins

(iii) NUMBER OF SEQUENCES: 51

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(B) COMPUTER:	IBM PS/2 Model 50Z or 55SX
(C) OPERATING SYSTEM:	IBM P.C. DOS (Version 3.30)
(D) SOFTWARE:	WordPerfect (Version 5.0)

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER:	07/637,830
(B) FILING DATE:	01/04/91
(C) CLASSIFICATION:	

(vii) PRIOR APPLICATION DATA:

Prior applications total, including application described below:	2
(A) APPLICATION NUMBER:	07/212,573
(B) FILING DATE:	28-06-88
(A) APPLICATION NUMBER:	07/539,842
(B) FILING DATE:	18-06-90

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(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(D) TOPOLOGY: LINEAR

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Ala Tyr Phe Gly Ala Ser Leu Cys Ser Val Asp Val Asp Ser Asn
5 10 15

Gly Ser Thr Asp Leu Val Leu Ile Gly Ala Pro
20 25

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(D) TOPOLOGY: LINEAR

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Gly Arg Phe Gly Ala Ala Leu Thr Val Leu Gly Asp Val Asn Gly
5 10 15

Asp Lys Leu Thr Asp Val Ala Ile Gly Ala Pro
20 25

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(D) TOPOLOGY: LINEAR

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Gln Tyr Phe Gly Gln Ser Leu Ser Gly Gly Gln Asp Leu Thr Met
5 10 15

Asp Gly Leu Val Asp Leu Thr Val Gly Ala Gln
20 25

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(D) TOPOLOGY: LINEAR

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Cys Pro Leu Pro
5 10 15

Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Val
20 25

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: LINEAR

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Asp Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His
5 10 15

Asp Phe Arg Arg Met Lys
20

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: LINEAR

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu Lys
5 10 15

Lys Ser Lys Thr Leu Phe
20

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Ser Leu Met Gln Tyr Ser Glu Glu Phe Arg Ile His Phe Thr Phe
5 10 15

Lys Glu Phe Gln Asn Asn
20

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Pro Asn Pro Arg Ser Leu Val Lys Pro Ile Thr Gln Leu Leu Gly
5 10 15

Arg Thr His Thr Ala Thr Gly Ile Arg Lys
20 25

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Arg Lys Val Val Arg Glu Leu Phe Asn Ile Thr Asn Gly Ala Arg
5 10 15

Lys Asn Ala Phe Lys
20

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu Lys Phe Gly Asp
5 10 15

Pro Leu Gly Tyr Glu Asp Val Ile Pro Glu Ala Asp Arg
20 25

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Arg Glu Gly Val Ile Arg Tyr Val Ile Gly Val Gly Asp Ala Phe
5 10 15

Arg Ser Glu Lys Ser Arg
20

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Gln Glu Leu Asn Thr Ile Ala Ser Lys Pro Pro Arg Asp His Val
5 10 15

Phe Gln Val Asn Asn Phe Glu
20

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Ala Leu Lys Thr Ile Gln Asn Gln Leu Arg Glu Lys Ile Phe Ala
5 10 15

Ile Glu Gly Thr

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Gln Thr Gly Ser Ser Ser Ser Phe Glu His Glu Met Ser Gln Glu
5 10 15

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Lys Ser Thr Arg Asp Arg Leu Arg
5

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Phe Arg Ser Glu Lys Ser Arg Gln Glu Leu Asn Thr Ile Ala Ser
5 10 15

Lys Pro Pro Arg Asp His Val
20

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly Tyr Glu Asp Val Ile
5 10 15

Pro Glu Ala Asp Arg
20

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Lys Glu Phe Gln Asn Asn Pro Asn Pro Arg Ser Leu
5 10

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18

(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Gly Thr Gln Thr Gly Ser Ser Ser Ser Phe Glu His Glu Met Ser
5 10 15

Gln Glu Gly

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Ser Asn Leu Arg Gln Gln Pro Gln Lys Phe Pro Glu Ala Leu Arg
5 10 15

Gly Cys Pro Gln Glu Asp Ser Asp
20

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Arg Gln Asn Thr Gly Met Trp Glu Ser Asn Ala Asn Val Lys Gly
5 10 15

Thr

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Thr Ser Gly Ser Gly Ile Ser Pro Ser His Ser Gln Arg Ile Ala
5 10 15

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr Gly Ser
5 10 15

Cys Glu Pro Ile Arg
20

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Pro Arg Gly Arg Ala Arg Trp Gln Cys
5

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Lys Leu Ser Pro Arg Leu Gln Tyr Phe Gly Gln Ser Leu Ser Gly
5 10 15

Gly Gln Asp Leu Thr
20

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Gln Lys Ser Thr Arg Asp Arg Leu Arg Glu Gly Gln
5 10

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Ser Gly Arg Pro His Ser Arg Ala Val Phe Asn Glu Thr Lys Asn
5 10 15

Ser Thr Arg Arg Gln Thr Gln
20

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Cys Glu Thr Leu Lys Leu Gln Leu Pro Asn Cys Ile Glu Asp Pro
5 10 15

Val

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Phe Glu Lys Asn Cys Gly Asn Asp Asn Ile Cys Gln Asp Asp Leu
5 10 15

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Val Arg Asn Asp Gly Glu Asp Ser Tyr Arg Thr Gln
5 10

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 31:

Ser Tyr Arg Lys Val Ser Thr Leu Gln Asn Gln Arg Ser Gln Arg
5 10 15
Ser

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Asp Ile Ala Phe Leu Ile Asp Gly Ser
5

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Phe Arg Arg Met Lys Glu Phe Val Ser
5

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu
5 10

(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Val Ile Arg Tyr Val Ile Gly Val Gly Asp Ala
5 10

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly
5 10

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Tyr Glu Asp Val Ile Pro Glu Ala Asp Arg
5 10

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Tyr Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Ser Val Cys
5 10 15

Pro Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Tyr
20 25

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5138
(B) TYPE: nucleic acid

(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

GAATTCCCTC TTTCACCCTG TCTAGGTTGC CAGCAAATCC CACGGGCCTC 50

CTGACGCTGC CCCTGgGGCC ACAgGTCCCT CGAGTGCTGG AAGG 94

ATG AAG GAT TCC TGC ATC ACT GTG ATG GCC ATG GCG CTG CTG TCT 139

GGG TTC TTT TTC TTC GCG CCG GCC TCG AGC TAC AAC CTG GAC GTG 184

CGG GGC GCG CGG AGC TTC TCC CCA CCG CGC GCC GGG AGG CAC TTT 229

GGA TAC CGC GTC CTG CAG GTC GGA AAC GGG GTC ATC GTG GGA GCT 274

CCA GGG GAG GGG AAC AGC ACA GGA AGC CTC TAT CAG TGC CAG TCG 319

GGC ACA GGA CAC TGC CTG CCA GTC ACC CTG AGA GGT TCC AAC TAT 364

ACC TCC AAG TAC TTG GGC ATG ACC TTG GCA ACA GAC CCC ACA GAT 409

GGA AGC ATT TTG GCC TGT GAC CCT GGG CTG TCT CGA ACG TGT GAC 454

CAG AAC ACC TAT CTG AGT GGC CTG TGT TAC CTC TTC CGC CAG AAT 499

CTG CAG GGT CCC ATG CTG CAG GGG CGC CCT GGT TTT CAG GAA TGT 544

ATC AAG GGC AAC GTA GAC CTG GTA TTT CTG TTT GAT GGT TCG ATG 589

AGC TTG CAG CCA GAT GAA TTT CAG AAA ATT CTG GAC TTC ATG AAG 634

GAT GTG ATG AAG AAA CTC AGC AAC ACT TCG TAC CAG TTT GCT GCT 679

GTT CAG TTT TCC ACA AGC TAC AAA ACA GAA TTT GAT TTC TCA GAT 724

TAT GTT AAA TGG AAG GAC CCT GAT GCT CTG CTG AAG CAT GTA AAG 769

CAC ATG TTG CTG TTG ACA AAT ACC TTT GGT GCC ATC AAT TAT GTC 814

GCG ACA GAG GTG TTC CGG GAG GAG CTG GGG GCC CGG CCA GAT GCC 859

ACC AAA GTG CTT ATC ATC ATC ACG GAT GGG GAG GCC ACT GAC AGT 904

GGC AAC ATC GAT GCG GCC AAA GAC ATC ATC CGC TAC ATC ATC GGG 949

ATT GGA AAG CAT TTT CAG ACC AAG GAG AGT CAG GAG ACC CTC CAC 994

AAA TTT GCA TCA AAA CCC GCG AGC GAG TTT GTG AAA ATT CTG GAC 1039

ACA TTT GAG AAG CTG AAA GAT CTA TTC ATC GAG CGG CAG AAG AAG 1084

ATC TAT GTC ATT GAG GGC ACA AGC AAA CAG GAC CTG ACT TCC TTC 1129

AAC ATG GAG CTG TCC TCC AGC GGC ATC AGT GCT GAC CTC AGC AGG 1174

GGC CAT GCA GTC GTG GGG GCA GTA GGA GCC AAG GAC TGG GCT GGG 1219

GGC TTT CTT GAC CTG AAG GCA GAC CTG CAG GAT GAC ACA TTT ATT 1264

GGG AAT GAA CCA TTG ACA CCA GAA GTG AGA GCA GGC TAT TTG GGT 1309

TAC ACC GTG ACC TGG CTG CCC TCC CGG CAA AAG ACT TCG TTG CTG 1354

GCC TCG GGA GCC CCT CGA TAC CAG CAC ATG GGC CGA GTG CTG CTG 1399

TTC CAA GAG CCA CAG GGC GGA GGA CAC TGG AGC CAG GTC CAG ACA 1444

ATC CAT GGG ACC CAG ATT GGC TCT TAT TTC GGT GGG GAG CTG TGT 1489

GGC GTC GAC GTG GAC CAA GAT GGG GAG ACA GAG CTG CTG CTG ATT 1534

GGT GCC CCA CTG TTC TAT GGG GAG CAG AGA GGA GGC CGG GTG TTT 1579

ACT CTG GAG CTG GTG GGA GAG ATC GAG GCC TCT TCC ATG TTC AGC 3244

CTC TGC AGC TCC CTC TCC ATC TCC TTC AAC AGC AGC AAG CAT TTC 3289

CAC CTC TAT GGC AGC AAC GCC TCC CTG GCC CAG GTT GTC ATG AAG 3334

GTT GAC GTG GTG TAT GAG AAG CAG ATG CTC TAC CTC TAC GTG CTG 3379

AGC GGC ATC GGG GGG CTG CTG CTG CTG CTG CTC ATT TNC ATA GTG 3424

CTG TAC AAG GTT GGT TTC TTC AAA CGG AAC CTG AAG GAG AAG ATG 3469

GAG GCT GGC AGA GGT GTC CCG AAT GGA ATC CCT GCA GAA GAC TCT 3514

GAG CAG CTG GCA TCT GGG CAA GAG GCT GGG GAT CCC GGC TGC CTG 3559

AAG CCC CTC CAT GAG AAG GAC TCT GAG AGT GGT GGT GGC AAG GAC 3604

TGAGTCCAGC CTGTGAGGTG CAGAGTGCCC AGAACTGGAC TCAGGATGCC 3654
CAGGGCCACT TCGCCTCTGC CTGCATTCTG CCGTGTGCCC TCGGGCGAGT 3704
CACTGCCTCT CCCTGGCCCT CAGTTTCCCT ATCTCGAACA TGGAACTCAT 3754
TCCTGAATGT CTCCTTTGCA GGCTCATAGG GAAGACCTGC TGAGGGACCA 3804
GCCAAGAGGG CTGCAAAAGT GAGGGCTTGT CATTACCAGA CGGTTCACCA 3854
GCCTCTCTTG GTTCCTTCCT TGGAAGAGAA TGTCTGATCT AAATGTGGAG 3904
AACTGTAGT CTCAGGACCT AGGGATGTTC TGGCCCTCAC CCCTGCCCTG 3954
GGATGTCCAC AGATGCCTCC ACCCCCCAGA ACCTGTCCTT GCACACTCCC 4004
CTGCACTGGA GTCCAGTCTC TTCTGTTGGC AGAAAGCAAA TGTGACCTGT 4054
GTCACTACGT GACTGTGGCA CACGCCTTGT TCTTGGCCAA AGACCAAATT 4104
CCTTGGCATG CCTTCCAGCA CCCTGCAAAA TGAGACCCTC GTGGCCTTCC 4154
CCAGCCTCTT CTAGAGCCGT GATGCCTCCC TGTTGAAGCT CTGGTGACAC 4204
CAGCCTTTCT CCCAGGCCAG GCTCCTTCCT GTCTTCCTGC ATTCACCCAG 4254
ACAGCTCCCT CTGCCTGAAC CTTCCATCTC GCCCACCCCT CCTTCCTTGA 4304
CCAGCAGATC CCAGCTCACG TCACACACTT GGTTGGGTCC TCACATCTTT 4354
CACACTTCCA CCACCCTGCA CTACTCCCTC AAAGCACACG TCATGTTTCT 4404
TCATCCGGCA GCCTGGATGT TTTTTCCCTG TTTAATGATT GACGTACTTA 4454
GCAGCTATCT CTCAGTGAAC TGTGAGGGTA AAGGCTATAC TTGTCTTGTT 4504
CACCTTGGGA TGACGCCGCA TGATATGTCA GGGCGTGGGA CATCTAGTAG 4554
GTGCTTGACA TAATTTCACT GAATTAATGA CAGAGCCAGT GGGAAGATAC 4604
AGAAAAAGAG GGCCGGGGCT GGGCGCGGTG GTTCACGCCT GTAATCCCAG 4654
CACTTTGGGA GGCCAAGGAG GGTGGATCAC CTGAGGTCAG GAGTTAGAGG 4704
CCAGCCTGGC GAAACCCCAT CTCTACTAAA AATACAAAAT CCAGGCGTGG 4754
TGGCACACAC CTGTAGTCCC AGCTACTCAG GAGGTTGAGG TAGGAGAATT 4804
GCTTGAACCT GGGAGGTGGA GGTTGCAGTG AGCCAAGATT GCGCCATTGC 4854
ACTCCAGCCT GGGCAACACA GCGAGACTCC GTCTCAAGGA AAAAATAAAA 4904

CCT TTT GAG AAG AAC TGT GGG GAG GAC AAG AAG TGT GAG GCA AAC 2434

TTG AGA GTG TCC TTC TCT CCT GCA ACA TCC AGA GCC CTG CGT CTA 2479

ACT GCT TTT GCC AGC CTC TCT GTG GAG CTG AGC CTG AGT AAC TTG 2524

GAA GAA GAT GCT TAC TGG GTC CAG CTG GAC CTG CAC TTC CCC CCG 2569

GGA CTC TCC TTC CGC AAG GTG GAG ATG CTG AAG CCC CAT AGC CAG 2614

ATA CCT GTG AGC TGC GAG GAG CTT CCT GAA GAG TCC AGG CTT CTG 2659

TCC AGG GCA TTA TCT TGC AAT GTG AGC TCT CCC ATC TTC AAA GCA 2704

GGC CAC TCG GTT GCT CTG CAG ATG ATG TTT AAT ACA CTG GTA AAC 2749

AGC TCC TGG GGG GAC TCG GTT GAA TTG CAC GCC AAT GTG ACC TGT 2794

AAC AAT GAG GAC TCA GAC CTC CTG GAG GAC AAC TCA GCC ACT ACC 2839

ATC ATC CCC ATC CTG TAC CCC ATC AAC ATC CTC ATC CAG GAC CAA 2884

GAA GAC TCC ACA CTC TAT GTC AGT TTC ACC CCC AAA GGC CCC AAG 2929

ATC CAC CAA GTC AAG CAC ATG TAC CAG GTG AGG ATC CAG CCT TCC 2974

ATC CAC GAC CAC AAC ATA CCC ACC CTG GAG GCT GTG GTT GGG GTG 3019

CCA CAG CCT CCC AGC GAG GGG CCC ATC ACA CAC CAG TGG AGC GTG 3064

CAG ATG GAG CCT CCC GTG CCC TGC CAC TAT GAG GAT CTG GAG AGG 3109

CTC CCG GAT GCA GCT GAG CCT TGT CTC CCC GGA CCC CTG TTC CGC 3154

TGC CCT GTT GTC TTC AGG CAG GAG ATC CTC GTC CAA GTG ATC GGG 3199

ATAAAAAGCG GGCACGGGCC CGGACATCCC CACCCTTGGA GGCTGTCTTC 4954
TCAGGCTCTG CCCTGCCCTA GCTCCACACC CTCTCCCAGG ACCCATCACG 5004
CCTGTGCAGT GGCCCCCACA GAAAGACTGA GCTCAAGGTG GGAACCACGT 5054
CTGCTAACTT GGAGCCCCAG TGCCAAGCAC AGTGCCTGCA TGTATTTATC 5104
CAATAAATGT GAAATTCTGT CCAAAAAAAA AAAA 5138

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 3533
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

tggcttcctt gtggttcctc agtggtgcct gcaacccctg gttcacctcc 50
ttccaggttc tggcccttcc agcc 74
atg gct ctc aga gtc ctt ctg tta aca gcc ttg acc tta tgt cat 119
ggg ttc aac ttg gac act gaa aac gca atg acc ttc caa gag aac 164
gca agg ggc ttc ggg cag agc gtg gtc cag ctt cag gga tcc agg 209

gtg gtg gtt gga gcc ccc cag gag ata gtg gct gcc aac caa agg 254

ggc agc ctc tac cag tgc gac tac agc aca ggc tca tgc gag ccc 299

atc cgc ctg cag gtc ccc gtg gag gcc gtg aac atg tcc ctg ggc 344

ctg tcc ctg gca gcc acc acc agc ccc cct cag ctg ctg gcc tgt 389

ggt ccc acc gtg cac cag act tgc agt gag aac acg tat gtg aaa 434

ggg ctc tgc ttc ctg ttt gga tcc aac cta cgg cag cag ccc cag 479

aag ttc cca gag gcc ctc cga ggg tgt cct caa gag gat agt gac 524

att gcc ttc ttg att gat ggc tct ggt agc atc atc cca cat gac 569

ttt cgg cgg atg aag gag ttt gtc tca act gtg atg gag caa tta 614

aaa aag tcc aaa acc ttg ttc tct ttg atg cag tac tct gaa gaa 659

ATC TAC CAG AGA AGA CAG TTG GGG TTT GAA GAA GTC TCA GAG CTG 1624

CAG GGG GAC CCC GGC TAC CCA CTC GGG CGG TTT GGA GAA GCC ATC 1669

ACT GCT CTG ACA GAC ATC AAC GGC GAT GGG CTG GTA GAC GTG GCT 1714

GTG GGG GCC CCT CTG GAG GAG CAG GGG GCT GTG TAC ATC TTC AAT 1759

GGG AGG CAC GGG GGG CTT AGT CCC CAG CCA AGT CAG CGG ATA GAA 1804

GGG ACC CAA GTG CTC TCA GGA ATT CAG TGG TTT GGA CGC TCC ATC 1849

CAT GGG GTG AAG GAC CTT GAA GGG GAT GGC CTG GCA GAT GTG GCT 1894

GTG GGG GCT GAG AGC CAG ATG ATC GTG CTG AGC TCC CGG CCC GTG 1939

GTG GAT ATG GTC ACC CTG ATG TCC TTC TCT CCA GCT GAG ATC CCA 1984

GTG CAT GAA GTG GAG TCG TCC TAT TCA ACC AGT AAC AAG ATG AAA 2029

GAA GGA GTT AAT ATC ACA ATC TGT TTC CAG ATC AAG TCT CTC TAC 2074

CCC CAG TTC CAA GGC CGC CTG GTT GCC AAT CTC ACT TAC ACT CTG 2119

CAG CTG GAT GGC CAC CGG ACC AGA AGA CGG GGG TTG TTC CCA GGA 2164

GGG AGA CAT GAA CTC AGA AGG AAT ATA GCT GTC ACC ACC AGC ATG 2209

TCA TGC ACT GAC TTC TCA TTT CAT TTC CCG GTA TGT GTT CAA GAC 2254

CTC ATC TCC CCC ATC AAT GTT TCC CTG AAT TTC TCT CTT TGG GAG 2299

GAG GAA GGG ACA CCG AGG GAC CAA AGG GCG CAG GGC AAG GAC ATA 2344

CCG CCC ATC CTG AGA CCC TCC CTG CAC TCG GAA ACC TGG GAG ATC 2389

ttc cgg att cac ttt acc ttc aaa gag ttc cag aac aac cct aac 704

cca aga tca ctg gtg aag cca ata acg cag ctg ctt ggg cgg aca 749

cac acg gcc acg ggc atc cgc aaa gtg gta cga gag ctg ttt aac 794

atc acc aac gga gcc cga aag aat gcc ttt aag atc cta gtt gtc 839

atc acg gat gga gaa aag ttt ggc gat ccc ttg gga tat gag gat 884

gtc atc cct gag gca gac aga gag gga gtc att cgc tac gtc att 929

ggg gtg gga gat gcc ttc cgc agt gag aaa tcc cgc caa gag ctt 974

aat acc atc gca tcc aag ccg cct cgt gat cac gtg ttc cag gtg 1019

aat aac ttt gag gct ctg aag acc att cag aac cag ctt cgg gag 1064

aag atc ttt gcg atc gag ggt act cag aca gga agt agc agc tcc 1109

ttt gag cat gag atg tct cag gaa ggc ttc agc gct gcc atc acc 1154

tct aat ggc ccc ttg ctg agc act gtg ggg agc tat gac tgg gct 1199

ggt gga gtc ttt cta tat aca tca aag gag aaa agc acc ttc atc 1244

aac atg acc aga gtg gat tca gac atg aat gat gct tac ttg ggt 1289

tat gct gcc gcc atc atc tta cgg aac cgg gtg caa agc ctg gtt 1334

ctg ggg gca cct cga tat cag cac atc ggc ctg gta gcg atg ttc 1379

agg cag aac act ggc atg tgg gag tcc aac gct aat gtc aag ggc 1424

acc cag atc ggc gcc tac ttc ggg gcc tcc ctc tgc tcc gtg gac 1469

gtg gac agc aac ggc agc acc gac ctg gtc ctc atc ggg gcc ccc 1514

cat tac tac gag cag acc cga ggg ggc cag gtg tcc gtg tgc ccc 1559

ttg ccc agg ggg agg gct cgg tgg cag tgt gat gct gtt ctc tac 1604

ggg gag cag ggc caa ccc tgg ggc cgc ttt ggg gca gcc cta aca 1649

gtg ctg ggg gac gta aat ggg gac aag ctg acg gac gtg gcc att 1694

ggg gcc cca gga gag gag gac aac cgg ggt gct gtt tac ctg ttt 1739

cac gga acc tca gga tct ggc atc agc ccc tcc cat agc cag cgg 1784

ata gca ggc tcc aag ctc tct ccc agg ctc cag tat ttt ggt cag 1829

tca ctg agt ggg ggc cag gac ctc aca atg gat gga ctg gta gac 1874

ctg act gta gga gcc cag ggg cac gtg ctg ctg ctc agg tcc cag 1919

cca gta ctg aga gtc aag gca atc atg gag ttc aat ccc agg gaa 1964

gtg gca agg aat gta ttt gag tgt aat gat caa gtg gtg aaa ggc 2002

aag gaa gcc gga gag gtc aga gtc tgc ctc cat gtc cag aag agc 2054

aca cgg gat cgg cta aga gaa gga cag atc cag agt gtt gtg act 2099

tat gac ctg gct ctg gac tcc ggc cgc cca cat tcc cgc gcc gtc 2144

ttc aat gag aca aag aac agc aca cgc aga cag aca cag gtc ttg 2189

ggg ctg acc cag act tgt gag acc ctg aaa cta cag ttg ccg aat 2234

tgc atc gag gac cca gtg agc ccc att gtg ctg cgc ctg aac ttc 2279

tct ctg gtg gga acg cca ttg tct gct ttc ggg aac ctc cgg cca 2324

gtg ctg gcg gag gat gct cag aga ctc ttc aca gcc ttg ttt ccc 2369

ttt gag aag aat tgt ggc aat gac aac atc tgc cag gat gac ctc 2414

agc atc acc ttc agt ttc atg agc ctg gac tgc ctc gtg gtg ggt 2459

ggg ccc cgg gag tct aac gtg aca gtg act gtg aga aat gat ggt 2504

gag gac tcc tac agg aca cag gtc acc ttc ttc ttc ccg ctt gac 2549

ctg tcc tac cgg aag gtg tcc aca ctc cag aac cag cgc tca cag 2594

cga tcc tgg cgc ctg gcc tgt gag tct gcc tcc tcc acc gaa gtg 2639

tct ggg gcc ttg aag agc acc agc tgc agc ata aac cac ccc atc 2684

ttc ccg gaa aac tca gag gtc acc ttt aat atc acg ttt gat gta 2729

gac tct aag gct tcc ctt gga aac aaa ctg ctc ctc aag gcc aat 2774

gtg acc agt gag aac aac atg ccc aga acc aac aaa acc gaa ttc 2819

caa ctg gag ctg ccg gtg aaa tat gct gtc tac atg gtg gtc acc 2864

agc cat ggg gtc tcc act aaa tat ctc aac ttc acg gcc tca gag 2909

aat acc agt cgg gtc atg cag cat caa tat cag gtc agc aac ctg 2954

ggg cag agg agc ccc ccc atc agc ctg gtg ttc ttg gtg ccc gtc 2999

cgg ctg aac cag act gtc ata tgg gac cgc ccc cag gtc acc ttc 3044

tcc gag aac ctc tcg agt acg tgc cac acc aag gag cgc ttg ccc 3089

tct cac tcc gac ttt ctg gct gag ctt cgg aag gcc ccc gtg gtg 3134

aac tgc tcc atc gct gtc tgc cag aga atc cag tgt gac atc ccg 3179

ttc ttt ggc atc cag gaa gaa ttc aat gct acc ctc aaa ggc aac 3224

ctc tcg ttt gac tgg tac atc aag acc tcg cat aac cac ctc ctg 3269

atc gtg agc aca gct gag atc ttg ttt aac gat tcc gtg ttc acc 3314

ctg ctg ccg gga cag ggg gcg ttt gtg agg tcc cag acg gag acc 3359

aaa gtg gag ccg ttc gag gtc ccc aac ccc ctg ccg ctc atc gtg 3404

ggc agc tct gtc ggg gga ctg ctg ctc ctg gcc ctc atc acc gcc 3449

gcg ctg tac aag ctc ggc ttc ttc aag cgg caa tac aag gac atg 3494

atg agt gaa ggg ggt ccc ccg ggg gcc gaa ccc cag tag 3533

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

(A)	LENGTH:	2310
(B)	TYPE:	nucleic acid
(C)	STRANDEDNESS:	single
(D)	TOPOLOGY:	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

ATG CTG GGC CTG CGC CCC CCA CTT CTC GCC CTG GTG GGG CTG CTC 45
TCC CTC GGG TGC GTC CTC TCT CAG GAG TGC ACG AAG TTC AAG GTC 90
AGC AGC TGC CGG GAA TGC ATC GAG TCG GGG CCC GGC TGC ACC TGG 135

TGC CAG AAG CTG AAC TTC ACA GGG CCG GGG GAT CCT GAC TCC ATT 180

CGC TGC GAC ACC CGG CCA CAG CTG CTC ATG AGG GGC TGT GCG GCT 225

GAC GAC ATC ATG GAC CCC ACA AGC CTC GCT GAA ACC CAG GAA GAC 270

CAC AAT GGG GGC CAG AAG CAG CTG TCC CCA CAA AAA GTG ACG CTT 315

TAC CTG CGA CCA GGC CAG GCA GCA GCG TTC AAC GTG ACC TTC CGG 360

CGG GCC AAG GGC TAC CCC ATC GAC CTG TAC TAT CTG ATG GAC CTC 405

TCC TAC TCC ATG CTT GAT GAC CTC AGG AAT GTC AAG AAG CTA GGT 450

GGC GAC CTG CTC CGG GCC CTC AAC GAG ATC ACC GAG TCC GGC CGC 495

ATT GGC TTC GGG TCC TTC GTG GAC AAG ACC GTG CTG CCG TTC GTG 540

AAC ACG CAC CCT GAT AAG CTG CGA AAC CCA TGC CCC AAC AAG GAG 585

AAA GAG TGC CAG CCC CCG TTT GCC TTC AGG CAC GTG CTG AAG CTG 630

ACC AAC AAC TCC AAC CAG TTT CAG ACC GAG GTC GGG AAG CAG CTG 675

ATT TCC GGA AAC CTG GAT GCA CCC GAG GGT GGG CTG GAC GCC ATG 720

ATG CAG GTC GCC GCC TGC CCG GAG GAA ATC GGC TGG CGC AAC GTC 765

ACG CGG CTG CTG GTG TTT GCC ACT GAT GAC GGC TTC CAT TTC GCG 810

GGC GAC GGA AAG CTG GGC GCC ATC CTG ACC CCC AAC GAC GGC CGC 855

TGT CAC CTG GAG GAC AAC TTG TAC AAG AGG AGC AAC GAA TTC GAC 900

TAC CCA TCG GTG GGC CAG CTG GCG CAC AAG CTG GCT GAA AAC AAC 945

ATC CAG CCC ATC TTC GCG GTG ACC AGT AGG ATG GTG AAG ACC TAC 990

GAG AAA CTC ACC GAG ATC ATC CCC AAG TCA GCC GTG GGG GAG CTG 1035

TCT GAG GAC TCC AGC AAT GTG GTC CAT CTC ATT AAG AAT GCT TAC 1080

AAT AAA CTC TCC TCC AGG GTC TTC CTG GAT CAC AAC GCC CTC CCC 1125

GAC ACC CTG AAA GTC ACC TAC GAC TCC TTC TGC AGC AAT GGA GTG 1170

ACG CAC AGG AAC CAG CCC AGA GGT GAC TGT GAT GGC GTG CAG ATC 1215

AAT GTC CCG ATC ACC TTC CAG GTG AAG GTC ACG GCC ACA GAG TGC 1260

ATC CAG GAG CAG TCG TTT GTC ATC CGG GCG CTG GGC TTC ACG GAC 1305

ATA GTG ACC GTG CAG GTT CTT CCC CAG TGT GAG TGC CGG TGC CGG 1350

GAC CAG AGC AGA GAC CGC AGC CTC TGC CAT GGC AAG GGC TTC TTG 1395

GAG TGC GGC ATC TGC AGG TGT GAC ACT GGC TAC ATT GGG AAA AAC 1440

TGT GAG TGC CAG ACA CAG GGC CGG AGC AGC CAG GAG CTG GAA GGA 1485

AGC TGC CGG AAG GAC AAC AAC TCC ATC ATC TGC TCA GGG CTG GGG 1530

GAC TGT GTC TGC GGG CAG TGC CTG TGC CAC ACC AGC GAC GTC CCC 1575

GGC AAG CTG ATA TAC GGG CAG TAC TGC GAG TGT GAC ACC ATC AAC 1620

TGT GAG CGC TAC AAC GGC CAG GTC TGC GGC GGC CCG GGG AGG GGG 1665

CTC TGC TTC TGC GGG AAG TGC CGC TGC CAC CCG GGC TTT GAG GGC 1710

TCA GCG TGC CAG TGC GAG AGG ACC ACT GAG GGC TGC CTG AAC CCG 1755

CGG CGT GTT GAG TGT AGT GGT CGT GGC CGG TGC CGC TGC AAC GTA 1800

TGC GAG TGC CAT TCA GGC TAC CAG CTG CCT CTG TGC CAG GAG TGC 1845

CCC GGC TGC CCC TCA CCC TGT GGC AAG TAC ATC TCC TGC GCC GAG 1890

TGC CTG AAG TTC GAA AAG GGC CCC TTT GGG AAG AAC TGC AGC GCG 1935

GCG TGT CCG GGC CTG CAG CTG TCG AAC AAC CCC GTG AAG GGC AGG 1980

ACC TGC AAG GAG AGG GAC TCA GAG GGC TGC TGG GTG GCC TAC ACG 2025

CTG GAG CAG CAG GAC GGG ATG GAC CGC TAC CTC ATC TAT GTG GAT 2070

GAG AGC CGA GAG TGT GTG GCA GGC CCC AAC ATC GCC GCC ATC GTC 2115

GGG GGC ACC GTG GCA GGC ATC GTG CTG ATC GGC ATT CTC CTG CTG 2160

GTC ATC TGG AAG GCT CTG ATC CAC CTG AGC GAC CTC CGG GAG TAC 2205

AGG CGC TTT GAG AAG GAG AAG CTC AAG TCC CAG TGG AAC AAT GAT 2250

AAT CCC CTT TTC AAG AGC GCC ACC ACG ACG GTC ATG AAC CCC AAG 2295

TTT GCT GAG AGT TAG 2310

(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1170
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

Met Lys Asp Ser Cys Ile Thr Val Met Ala Met Ala Leu Leu Ser
5 10 15

Gly Phe Phe Phe Phe Ala Pro Ala Ser Ser Tyr Asn Leu Asp Val
20 25 30

Arg Gly Ala Arg Ser Phe Ser Pro Pro Arg Ala Gly Arg His Phe
35 40 50

Gly Tyr Arg Val Leu Gln Val Gly Asn Gly Val Ile Val Gly Ala
55 60 65

Pro Gly Glu Gly Asn Ser Thr Gly Ser Leu Tyr Gln Cys Gln Ser

70 75 80

Gly Thr Gly His Cys Leu Pro Val Thr Leu Arg Gly Ser Asn Tyr
85 90 95

Thr Ser Lys Tyr Leu Gly Met Thr Leu Ala Thr Asp Pro Thr Asp
100 105 115

Gly Ser Ile Leu Ala Cys Asp Pro Gly Leu Ser Arg Thr Cys Asp
120 125 130

Gln Asn Thr Tyr Leu Ser Gly Leu Cys Tyr Leu Phe Arg Gln Asn
135 140 145

Leu Gln Gly Pro Met Leu Gln Gly Arg Pro Gly Phe Gln Glu Cys
150 155 160

Ile Lys Gly Asn Val Asp Leu Val Phe Leu Phe Asp Gly Ser Met
165 170 175

Ser Leu Gln Pro Asp Glu Phe Gln Lys Ile Leu Asp Phe Met Lys
180 185 190

Asp Val Met Lys Lys Leu Ser Asn Thr Ser Tyr Gln Phe Ala Ala
195 200 205

Val Gln Phe Ser Thr Ser Tyr Lys Thr Glu Phe Asp Phe Ser Asp
215 220 225

Tyr Val Lys Trp Lys Asp Pro Asp Ala Leu Leu Lys His Val Lys
230 235 240

His Met Leu Leu Leu Thr Asn Thr Phe Gly Ala Ile Asn Tyr Val
245 250 255

Ala Thr Glu Val Phe Arg Glu Glu Leu Gly Ala Arg Pro Asp Ala
260 265 270

Thr Lys Val Leu Ile Ile Ile Thr Asp Gly Glu Ala Thr Asp Ser
275 280 285

Gly Asn Ile Asp Ala Ala Lys Asp Ile Ile Arg Tyr Ile Ile Gly
290 295 300

Ile Gly Lys His Phe Gln Thr Lys Glu Ser Gln Glu Thr Leu His
305 310 315

Lys Phe Ala Ser Lys Pro Ala Ser Glu Phe Val Lys Ile Leu Asp
320 325 330

Thr Phe Glu Lys Leu Lys Asp Leu Phe Ile Glu Arg Gln Lys Lys
335 340 345

Ile Tyr Val Ile Glu Gly Thr Ser Lys Gln Asp Leu Thr Ser Phe

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                    350                 355                 360

Asn Met Glu Leu Ser Ser Ser Gly Ile Ser Ala Asp Leu Ser Arg
                365                 370                 375

Gly His Ala Val Val Gly Ala Val Gly Ala Lys Asp Trp Ala Gly
                380                 385                 390

Gly Phe Leu Asp Leu Lys Ala Asp Leu Gln Asp Asp Thr Phe Ile
                395                 400                 405

Gly Asn Glu Pro Leu Thr Pro Glu Val Arg Ala Gly Tyr Leu Gly
                415                 420                 425

Tyr Thr Val Thr Trp Leu Pro Ser Arg Gln Lys Thr Ser Leu Leu
                430                 435                 440

Ala Ser Gly Ala Pro Arg Tyr Gln His Met Gly Arg Val Leu Leu
                445                 450                 455

Phe Gln Glu Pro Gln Gly Gly Gly His Trp Ser Gln Val Gln Thr
                460                 465                 470

Ile His Gly Thr Gln Ile Gly Ser Tyr Phe Gly Gly Glu Leu Cys
                475                 480                 485

Gly Val Asp Val Asp Gln Asp Gly Glu Thr Glu Leu Leu Leu Ile
                490                 495                 500

Gly Ala Pro Leu Phe Tyr Gly Glu Gln Arg Gly Gly Arg Val Phe
                505                 510                 515

Ile Tyr Gln Arg Arg Gln Leu Gly Phe Glu Glu Val Ser Glu Leu
                520                 525                 530

Gln Gly Asp Pro Gly Tyr Pro Leu Gly Arg Phe Gly Glu Ala Ile
                535                 540                 545

Thr Ala Leu Thr Asp Ile Asn Gly Asp Gly Leu Val Asp Val Ala
                550                 555                 560

Val Gly Ala Pro Leu Glu Glu Gln Gly Ala Val Tyr Ile Phe Asn
                565                 570                 575

Gly Arg His Gly Gly Leu Ser Pro Gln Pro Ser Gln Arg Ile Glu
                580                 585                 590

Gly Thr Gln Val Leu Ser Gly Ile Gln Trp Phe Gly Arg Ser Ile
                595                 600                 605

His Gly Val Lys Asp Leu Glu Gly Asp Gly Leu Ala Asp Val Ala
                610                 615                 620

Val Gly Ala Glu Ser Gln Met Ile Val Leu Ser Ser Arg Pro Val
```

625 630 635

Val Asp Met Val Thr Leu Met Ser Phe Ser Pro Ala Glu Ile Pro
640 645 650

Val His Glu Val Glu Ser Ser Tyr Ser Thr Ser Asn Lys Met Lys
655 670 675

Glu Gly Val Asn Ile Thr Ile Cys Phe Gln Ile Lys Ser Leu Tyr
680 685 690

Pro Gln Phe Gln Gly Arg Leu Val Ala Asn Leu Thr Tyr Thr Leu
695 670 675

Gln Leu Asp Gly His Arg Thr Arg Arg Arg Gly Leu Phe Pro Gly
680 685 690

Gly Arg His Glu Leu Arg Arg Asn Ile Ala Val Thr Thr Ser Met
695 700 705

Ser Cys Thr Asp Phe Ser Phe His Phe Pro Val Cys Val Gln Asp
710 715 720

Leu Ile Ser Pro Ile Asn Val Ser Leu Asn Phe Ser Leu Trp Glu
725 730 735

Glu Glu Gly Thr Pro Arg Asp Gln Arg Ala Gln Gly Lys Asp Ile
740 745 750

Pro Pro Ile Leu Arg Pro Ser Leu His Ser Glu Thr Trp Glu Ile
755 760 765

Pro Phe Glu Lys Asn Cys Gly Glu Asp Lys Lys Cys Glu Ala Asn
770 775 780

Leu Arg Val Ser Phe Ser Pro Ala Thr Ser Arg Ala Leu Arg Leu
785 790 795

Thr Ala Phe Ala Ser Leu Ser Val Glu Leu Ser Leu Ser Asn Leu
800 805 810

Glu Glu Asp Ala Tyr Trp Val Gln Leu Asp Leu His Phe Pro Pro
815 820 825

Gly Leu Ser Phe Arg Lys Val Glu Met Leu Lys Pro His Ser Gln
830 835 840

Ile Pro Val Ser Cys Glu Glu Leu Pro Glu Glu Ser Arg Leu Leu
845 850 855

Ser Arg Ala Leu Ser Cys Asn Val Ser Ser Pro Ile Phe Lys Ala
860 865 870

Gly His Ser Val Ala Leu Gln Met Met Phe Asn Thr Leu Val Asn

875 880 885

Ser Ser Trp Gly Asp Ser Val Glu Leu His Ala Asn Val Thr Cys
890 895 900

Asn Asn Glu Asp Ser Asp Leu Leu Glu Asp Asn Ser Ala Thr Thr
905 910 915

Ile Ile Pro Ile Leu Tyr Pro Ile Asn Ile Leu Ile Gln Asp Gln
920 925 930

Glu Asp Ser Thr Leu Tyr Val Ser Phe Thr Pro Lys Gly Pro Lys
935 940 945

Ile His Gln Val Lys His Met Tyr Gln Val Arg Ile Gln Pro Ser
950 955 960

Ile His Asp His Asn Ile Pro Thr Leu Glu Ala Val Val Gly Val
965 970 975

Pro Gln Pro Pro Ser Glu Gly Pro Ile Thr His Gln Trp Ser Val
980 985 990

Gln Met Glu Pro Pro Val Pro Cys His Tyr Glu Asp Leu Glu Arg
995 1000 1005

Leu Pro Asp Ala Ala Glu Pro Cys Leu Pro Gly Pro Leu Phe Arg
1010 1015 1020

Cys Pro Val Val Phe Arg Gln Glu Ile Leu Val Gln Val Ile Gly
1025 1030 1035

Thr Leu Glu Leu Val Gly Glu Ile Glu Ala Ser Ser Met Phe Ser
1040 1045 1050

Leu Cys Ser Ser Leu Ser Ile Ser Phe Asn Ser Ser Lys His Phe
1055 1060 1065

His Leu Tyr Gly Ser Asn Ala Ser Leu Ala Gln Val Val Met Lys
1070 1075 1080

Val Asp Val Val Tyr Glu Lys Gln Met Leu Tyr Leu Tyr Val Leu
1085 1090 1095

Ser Gly Ile Gly Gly Leu Leu Leu Leu Leu Leu Ile Xaa Ile Val
1100 1105 1110

Leu Tyr Lys Val Gly Phe Phe Lys Arg Asn Leu Lys Glu Lys Met
1115 1120 1125

Glu Ala Gly Arg Gly Val Pro Asn Gly Ile Pro Ala Glu Asp Ser
1130 1135 1140

Glu Gln Leu Ala Ser Gly Gln Glu Ala Gly Asp Pro Gly Cys Leu

1145 1150 1155

Lys Pro Leu His Glu Lys Asp Ser Glu Ser Gly Gly Gly Lys Asp
1160 1165 1170

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1152
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Met Ala Leu Arg Val Leu Leu Leu Thr Ala Leu Thr Leu Cys His
5 10 15

Gly Phe Asn Leu Asp Thr Glu Asn Ala Met Thr Phe Gln Glu Asn
20 25 30

Ala Arg Gly Phe Gly Gln Ser Val Val Gln Leu Gln Gly Ser Arg
35 40 50

Val Val Val Gly Ala Pro Gln Glu Ile Val Ala Ala Asn Gln Arg
55 60 65

Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr Gly Ser Cys Glu Pro
70 75 80

Ile Arg Leu Gln Val Pro Val Glu Ala Val Asn Met Ser Leu Gly
85 90 95

Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu Leu Ala Cys
100 105 115

Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr Val Lys
120 125 130

Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro Gln
135 140 145

Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp
150 155 160

Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His Asp
165 170 175

Phe Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu
180 185 190

Lys Lys Ser Lys Thr Leu Phe Ser Leu Met Gln Tyr Ser Glu Glu
195 200 205

Phe Arg Ile His Phe Thr Phe Lys Glu Phe Gln Asn Asn Pro Asn
215 220 225

Pro Arg Ser Leu Val Lys Pro Ile Thr Gln Leu Leu Gly Arg Thr
230 235 240

His Thr Ala Thr Gly Ile Arg Lys Val Val Arg Glu Leu Phe Asn
245 250 255

Ile Thr Asn Gly Ala Arg Lys Asn Ala Phe Lys Ile Leu Val Val
260 265 270

Ile Thr Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly Tyr Glu Asp
275 280 285

Val Ile Pro Glu Ala Asp Arg Glu Gly Val Ile Arg Tyr Val Ile
290 295 300

Gly Val Gly Asp Ala Phe Arg Ser Glu Lys Ser Arg Gln Glu Leu
305 310 315

Asn Thr Ile Ala Ser Lys Pro Pro Arg Asp His Val Phe Gln Val
320 325 330

Asn Asn Phe Glu Ala Leu Lys Thr Ile Gln Asn Gln Leu Arg Glu
335 340 345

Lys Ile Phe Ala Ile Glu Gly Thr Gln Thr Gly Ser Ser Ser Ser
350 355 360

Phe Glu His Glu Met Ser Gln Glu Gly Phe Ser Ala Ala Ile Thr
365 370 375

Ser Asn Gly Pro Leu Leu Ser Thr Val Gly Ser Tyr Asp Trp Ala
380 385 390

Gly Gly Val Phe Leu Tyr Thr Ser Lys Glu Lys Ser Thr Phe Ile
395 400 405

Asn Met Thr Arg Val Asp Ser Asp Met Asn Asp Ala Tyr Leu Gly
415 420 425

Tyr Ala Ala Ala Ile Ile Leu Arg Asn Arg Val Gln Ser Leu Val
430 435 440

Leu Gly Ala Pro Arg Tyr Gln His Ile Gly Leu Val Ala Met Phe
445 450 455

Arg Gln Asn Thr Gly Met Trp Glu Ser Asn Ala Asn Val Lys Gly
460 465 470

Thr Gln Ile Gly Ala Tyr Phe Gly Ala Ser Leu Cys Ser Val Asp
475 480 485

Val Asp Ser Asn Gly Ser Thr Asp Leu Val Leu Ile Gly Ala Pro
490 495 500

His Tyr Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Cys Pro
505 510 515

Leu Pro Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Val Leu Tyr
520 525 530

Gly Glu Gln Gly Gln Pro Trp Gly Arg Phe Gly Ala Ala Leu Thr
535 540 545

Val Leu Gly Asp Val Asn Gly Asp Lys Leu Thr Asp Val Ala Ile
550 555 560

Gly Ala Pro Gly Glu Glu Asp Asn Arg Gly Ala Val Tyr Leu Phe
565 570 575

His Gly Thr Ser Gly Ser Gly Ile Ser Pro Ser His Ser Gln Arg
580 585 590

Ile Ala Gly Ser Lys Leu Ser Pro Arg Leu Gln Tyr Phe Gly Gln
595 600 605

Ser Leu Ser Gly Gly Gln Asp Leu Thr Met Asp Gly Leu Val Asp
610 615 620

Leu Thr Val Gly Ala Gln Gly His Val Leu Leu Leu Arg Ser Gln
625 630 635

Pro Val Leu Arg Val Lys Ala Ile Met Glu Phe Asn Pro Arg Glu
640 645 650

Val Ala Arg Asn Val Phe Glu Cys Asn Asp Gln Val Val Lys Gly
655 670 675

Lys Glu Ala Gly Glu Val Arg Val Cys Leu His Val Gln Lys Ser
680 685 690

Thr Arg Asp Arg Leu Arg Glu Gly Gln Ile Gln Ser Val Val Thr
695 670 675

Tyr Asp Leu Ala Leu Asp Ser Gly Arg Pro His Ser Arg Ala Val
680 685 690

Phe Asn Glu Thr Lys Asn Ser Thr Arg Arg Gln Thr Gln Val Leu
695 700 705

Gly Leu Thr Gln Thr Cys Glu Thr Leu Lys Leu Gln Leu Pro Asn
710 715 720

Cys Ile Glu Asp Pro Val Ser Pro Ile Val Leu Arg Leu Asn Phe
725 730 735

Ser Leu Val Gly Thr Pro Leu Ser Ala Phe Gly Asn Leu Arg Pro
740 745 750

Val Leu Ala Glu Asp Ala Gln Arg Leu Phe Thr Ala Leu Phe Pro
755 760 765

Phe Glu Lys Asn Cys Gly Asn Asp Asn Ile Cys Gln Asp Asp Leu
770 775 780

Ser Ile Thr Phe Ser Phe Met Ser Leu Asp Cys Leu Val Val Gly
785 790 795

Gly Pro Arg Glu Ser Asn Val Thr Val Thr Val Arg Asn Asp Gly
800 805 810

Glu Asp Ser Tyr Arg Thr Gln Val Thr Phe Phe Phe Pro Leu Asp
815 820 825

Leu Ser Tyr Arg Lys Val Ser Thr Leu Gln Asn Gln Arg Ser Gln
830 835 840

Arg Ser Trp Arg Leu Ala Cys Glu Ser Ala Ser Ser Thr Glu Val
845 850 855

Ser Gly Ala Leu Lys Ser Thr Ser Cys Ser Ile Asn His Pro Ile
860 865 870

Phe Pro Glu Asn Ser Glu Val Thr Phe Asn Ile Thr Phe Asp Val
875 880 885

Asp Ser Lys Ala Ser Leu Gly Asn Lys Leu Leu Leu Lys Ala Asn
890 895 900

Val Thr Ser Glu Asn Asn Met Pro Arg Thr Asn Lys Thr Glu Phe
905 910 915

Gln Leu Glu Leu Pro Val Lys Tyr Ala Val Tyr Met Val Val Thr
920 925 930

Ser His Gly Val Ser Thr Lys Tyr Leu Asn Phe Thr Ala Ser Glu
935 940 945

Asn Thr Ser Arg Val Met Gln His Gln Tyr Gln Val Ser Asn Leu
950 955 960

Gly Gln Arg Ser Pro Pro Ile Ser Leu Val Phe Leu Val Pro Val
965 970 975

Arg Leu Asn Gln Thr Val Ile Trp Asp Arg Pro Gln Val Thr Phe
980 985 990

Ser Glu Asn Leu Ser Ser Thr Cys His Thr Lys Glu Arg Leu Pro
995 1000 1005

Ser His Ser Asp Phe Leu Ala Glu Leu Arg Lys Ala Pro Val Val
1010 1015 1020

Asn Cys Ser Ile Ala Val Cys Gln Arg Ile Gln Cys Asp Ile Pro
1025 1030 1035

Phe Phe Gly Ile Gln Glu Glu Phe Asn Ala Thr Leu Lys Gly Asn
1040 1045 1050

Leu Ser Phe Asp Trp Tyr Ile Lys Thr Ser His Asn His Leu Leu
1055 1060 1065

Ile Val Ser Thr Ala Glu Ile Leu Phe Asn Asp Ser Val Phe Thr
1070 1075 1080

Leu Leu Pro Gly Gln Gly Ala Phe Val Arg Ser Gln Thr Glu Thr
1085 1090 1095

Lys Val Glu Pro Phe Glu Val Pro Asn Pro Leu Pro Leu Ile Val
1100 1105 1110

Gly Ser Ser Val Gly Gly Leu Leu Leu Leu Ala Leu Ile Thr Ala
1115 1120 1125

Ala Leu Tyr Lys Leu Gly Phe Phe Lys Arg Gln Tyr Lys Asp Met
1130 1135 1140

Met Ser Glu Gly Gly Pro Pro Gly Ala Glu Pro Gln
1145 1150

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1163
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Met Thr Arg Thr Arg Ala Ala Leu Leu Leu Phe Thr Ala Leu Ala
5 10 15

Thr Ser Leu Gly Phe Asn Leu Asp Thr Glu Glu Leu Thr Ala Phe
20 25 30

Arg Val Asp Ser Ala Gly Phe Gly Asp Ser Val Val Gln Tyr Ala
35 40 50

Asn Ser Trp Val Val Val Gly Ala Pro Gln Lys Ile Thr Ala Ala
55 60 65

Asn Gln Thr Gly Gly Leu Tyr Gln Cys Gly Tyr Ser Thr Gly Ala
70 75 80

Cys Glu Pro Ile Gly Leu Gln Val Pro Pro Glu Ala Val Asn Met
85 90 95

Ser Leu Gly Leu Ser Leu Ala Ser Thr Thr Ser Pro Ser Gln Leu
100 105 115

Leu Ala Cys Gly Pro Thr Val His His Glu Cys Gly Arg Asn Met
120 125 130

Tyr Leu Thr Gly Leu Cys Phe Leu Leu Gly Pro Thr Gln Leu Thr
135 140 145

Gln Arg Leu Pro Val Ser Arg Gln Glu Cys Pro Arg Gln Glu Gln
150 155 160

Asp Ile Val Phe Leu Ile Asp Gly Ser Gly Ser Ile Ser Ser Arg
165 170 175

Asn Phe Ala Thr Met Met Asn Phe Val Arg Ala Val Ile Ser Gln
180 185 190

Phe Gln Arg Pro Ser Thr Gln Phe Ser Leu Met Gln Phe Ser Asn
195 200 205

Lys Phe Gln Thr His Phe Thr Phe Glu Glu Phe Arg Arg Thr Ser
215 220 225

Asn Pro Leu Ser Leu Leu Ala Ser Val His Gln Leu Gln Gly Phe
230 235 240

Thr Tyr Thr Ala Thr Ala Ile Gln Asn Val Val His Arg Leu Phe
245 250 255

His Ala Ser Tyr Gly Ala Arg Arg Asp Ala Thr Lys Ile Leu Ile
260 265 270

Val Ile Thr Asp Gly Lys Lys Glu Gly Asp Ser Leu Asp Tyr Lys
275 280 285

Asp Val Ile Pro Met Ala Asp Ala Ala Gly Ile Ile Arg Tyr Ala
290 295 300

Ile Gly Val Gly Leu Ala Phe Gln Asn Arg Asn Ser Trp Lys Glu
305 310 315

Leu Asn Asp Ile Ala Ser Lys Pro Ser Gln Glu His Ile Phe Lys
320 325 330

Val Glu Asp Phe Asp Ala Leu Lys Asp Ile Gln Asn Gln Leu Lys
335 340 345

Glu Lys Ile Phe Ala Ile Glu Gly Thr Glu Thr Thr Ser Ser Ser
350 355 360

Ser Phe Glu Leu Glu Met Ala Gln Glu Gly Phe Ser Ala Val Phe
365 370 375

Thr Pro Asp Gly Pro Val Leu Gly Ala Val Gly Ser Phe Thr Trp
380 385 390

Ser Gly Gly Ala Phe Leu Tyr Pro Pro Asn Met Ser Pro Thr Phe
395 400 405

Ile Asn Met Ser Gln Glu Asn Val Asp Met Arg Asp Ser Tyr Leu
415 420 425

Gly Tyr Ser Thr Glu Leu Ala Leu Trp Lys Gly Val Gln Ser Leu
430 435 440

Val Leu Gly Ala Pro Arg Tyr Gln His Thr Gly Lys Ala Val Ile
445 450 455

Phe Thr Gln Val Ser Arg Gln Trp Arg Met Lys Ala Glu Val Thr
460 465 470

Gly Thr Gln Ile Gly Ser Tyr Phe Gly Ala Ser Leu Cys Ser Val
475 480 485

Asp Val Asp Thr Asp Gly Ser Thr Asp Leu Val Leu Ile Gly Ala
490 495 500

Pro His Tyr Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Cys
505 510 515

Pro Leu Pro Arg Gly Trp Arg Arg Trp Trp Cys Asp Ala Val Leu
520 525 530

Tyr Gly Glu Gln Gly His Pro Trp Gly Arg Phe Gly Ala Ala Leu
535 540 545

Thr Val Leu Gly Asp Val Asn Gly Asp Lys Leu Thr Asp Val Val
550 555 560

Ile Gly Ala Pro Gly Glu Glu Glu Asn Arg Gly Ala Val Tyr Leu
565 570 575

Phe His Gly Val Leu Gly Pro Ser Ile Ser Pro Ser His Ser Gln
580 585 590

Arg Ile Ala Gly Ser Gln Leu Ser Ser Arg Leu Gln Tyr Phe Gly
595 600 605

Gln Ala Leu Ser Gly Gly Gln Asp Leu Thr Gln Asp Gly Leu Val
610 615 620

Asp Leu Ala Val Gly Ala Arg Gly Gln Val Leu Leu Leu Arg Thr
625 630 635

Arg Pro Val Leu Trp Val Gly Val Ser Met Gln Phe Ile Pro Ala
640 645 650

Glu Ile Pro Arg Ser Ala Phe Glu Cys Arg Glu Gln Val Val Ser
655 670 675

Glu Gln Thr Leu Val Gln Ser Asn Ile Cys Leu Tyr Ile Asp Lys
680 685 690

Arg Ser Lys Asn Leu Leu Gly Ser Arg Asp Leu Gln Ser Ser Val
695 670 675

Thr Leu Asp Leu Ala Leu Asp Pro Gly Arg Leu Ser Pro Arg Ala
680 685 690

Thr Phe Gln Glu Thr Lys Asn Arg Ser Leu Ser Arg Val Arg Val
695 700 705

Leu Gly Leu Lys Ala His Cys Glu Asn Phe Asn Leu Leu Leu Pro
710 715 720

Ser Cys Val Glu Asp Ser Val Thr Pro Ile Thr Leu Arg Leu Asn
725 730 735

Phe Thr Leu Val Gly Lys Pro Leu Leu Ala Phe Arg Asn Leu Arg
740 745 750

Pro Met Leu Ala Ala Leu Ala Gln Arg Tyr Phe Thr Ala Ser Leu
755 760 765

Pro Phe Glu Lys Asn Cys Gly Ala Asp His Ile Cys Gln Asp Asn
770 775 780

Leu Gly Ile Ser Phe Ser Phe Pro Gly Leu Lys Ser Leu Leu Val
785 790 795

Gly Ser Asn Leu Glu Leu Asn Ala Glu Val Met Val Trp Asn Asp
800 805 810

Gly Glu Asp Ser Tyr Gly Thr Thr Ile Thr Phe Ser His Pro Ala
815 820 825

Gly Leu Ser Tyr Arg Tyr Val Ala Glu Gly Gln Lys Gln Gly Gln
830 835 840

Leu Arg Ser Leu His Leu Thr Cys Asp Ser Ala Pro Val Gly Ser
845 850 855

Gln Gly Thr Trp Ser Thr Ser Cys Arg Ile Asn His Leu Ile Phe
860 865 870

Arg Gly Gly Ala Gln Ile Thr Phe Leu Ala Thr Phe Asp Val Ser
875 880 885

Pro Lys Ala Val Leu Gly Asp Arg Leu Leu Leu Thr Ala Asn Val
890 895 900

Ser Ser Glu Asn Asn Thr Pro Arg Thr Ser Lys Thr Thr Phe Gln
905 910 915

Leu Glu Leu Pro Val Lys Tyr Ala Val Tyr Thr Val Val Ser Ser
920 925 930

His Glu Gln Phe Thr Lys Tyr Leu Asn Phe Ser Glu Ser Glu Glu
935 940 945

Lys Glu Ser His Val Ala Met His Arg Tyr Gln Val Asn Asn Leu
950 955 960

Gly Gln Arg Asp Leu Pro Val Ser Ile Asn Phe Trp Val Pro Val
965 970 975

Glu Leu Asn Gln Glu Ala Val Trp Met Asp Val Glu Val Ser His
980 985 990

Pro Gln Asn Pro Ser Leu Arg Cys Ser Ser Glu Lys Ile Ala Pro
995 1000 1005

Pro Ala Ser Asp Phe Leu Ala His Ile Gln Lys Asn Pro Val Leu
1010 1015 1020

Asp Cys Ser Ile Ala Gly Cys Leu Arg Phe Arg Cys Asp Val Pro
1025 1030 1035

Ser Phe Ser Val Gln Glu Glu Leu Asp Phe Thr Leu Lys Gly Asn
1040 1045 1050

Leu Ser Phe Gly Trp Val Arg Gln Ile Leu Gln Lys Lys Val Ser
1055 1060 1065

Val Val Ser Val Ala Glu Ile Thr Phe Asp Thr Ser Val Tyr Ser
1070 1075 1080

Gln Leu Pro Gly Gln Glu Ala Phe Met Arg Ala Gln Thr Thr Thr
1085 1090 1095

Val Leu Glu Lys Tyr Lys Val His Asn Pro Thr Pro Leu Ile Val
1100 1105 1110

Gly Ser Ser Ile Gly Gly Leu Leu Leu Leu Ala Leu Ile Thr Ala
1115 1120 1125

Val Leu Tyr Lys Val Gly Phe Phe Lys Arg Gln Tyr Lys Glu Met
1130 1135 1140

Met Glu Glu Ala Asn Gly Gln Ile Ala Pro Glu Asn Gly Thr Gln
1145 1150 1155

Thr Pro Ser Pro Pro Ser Glu Lys
1160

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 769
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Met Leu Gly Leu Arg Pro Pro Leu Leu Ala Leu Val Gly Leu Leu
5 10 15

Ser Leu Gly Cys Val Leu Ser Gln Glu Cys Thr Lys Phe Lys Val
20 25 30

Ser Ser Cys Arg Glu Cys Ile Glu Ser Gly Pro Gly Cys Thr Trp
35 40 50

Cys Gln Lys Leu Asn Phe Thr Gly Pro Gly Asp Pro Asp Ser Ile
55 60 65

Arg Cys Asp Thr Arg Pro Gln Leu Leu Met Arg Gly Cys Ala Ala
70 75 80

Asp Asp Ile Met Asp Pro Thr Ser Leu Ala Glu Thr Gln Glu Asp
85 90 95

His Asn Gly Gly Gln Lys Gln Leu Ser Pro Gln Lys Val Thr Leu
100 105 115

Tyr Leu Arg Pro Gly Gln Ala Ala Ala Phe Asn Val Thr Phe Arg
120 125 130

Arg Ala Lys Gly Tyr Pro Ile Asp Leu Tyr Tyr Leu Met Asp Leu
135 140 145

Ser Tyr Ser Met Leu Asp Asp Leu Arg Asn Val Lys Lys Leu Gly
150 155 160

Gly Asp Leu Leu Arg Ala Leu Asn Glu Ile Thr Glu Ser Gly Arg
165 170 175

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Ile Gly Phe Gly Ser Phe Val Asp Lys Thr Val Leu Pro Phe Val
                180                 185                 190

Asn Thr His Pro Asp Lys Leu Arg Asn Pro Cys Pro Asn Lys Glu
                195                 200                 205

Lys Glu Cys Gln Pro Pro Phe Ala Phe Arg His Val Leu Lys Leu
                215                 220                 225

Thr Asn Asn Ser Asn Gln Phe Gln Thr Glu Val Gly Lys Gln Leu
                230                 235                 240

Ile Ser Gly Asn Leu Asp Ala Pro Glu Gly Gly Leu Asp Ala Met
                245                 250                 255

Met Gln Val Ala Ala Cys Pro Glu Glu Ile Gly Trp Arg Asn Val
                260                 265                 270

Thr Arg Leu Leu Val Phe Ala Thr Asp Asp Gly Phe His Phe Ala
                275                 280                 285

Gly Asp Gly Lys Leu Gly Ala Ile Leu Thr Pro Asn Asp Gly Arg
                290                 295                 300

Cys His Leu Glu Asp Asn Leu Tyr Lys Arg Ser Asn Glu Phe Asp
                305                 310                 315

Tyr Pro Ser Val Gly Gln Leu Ala His Lys Leu Ala Glu Asn Asn
                320                 325                 330

Ile Gln Pro Ile Phe Ala Val Thr Ser Arg Met Val Lys Thr Tyr
                335                 340                 345

Glu Lys Leu Thr Glu Ile Ile Pro Lys Ser Ala Val Gly Glu Leu
                350                 355                 360

Ser Glu Asp Ser Ser Asn Val Val His Leu Ile Lys Asn Ala Tyr
                365                 370                 375

Asn Lys Leu Ser Ser Arg Val Phe Leu Asp His Asn Ala Leu Pro
                380                 385                 390

Asp Thr Leu Lys Val Thr Tyr Asp Ser Phe Cys Ser Asn Gly Val
                395                 400                 405

Thr His Arg Asn Gln Pro Arg Gly Asp Cys Asp Gly Val Gln Ile
                415                 420                 425

Asn Val Pro Ile Thr Phe Gln Val Lys Val Thr Ala Thr Glu Cys
                430                 435                 440

Ile Gln Glu Gln Ser Phe Val Ile Arg Ala Leu Gly Phe Thr Asp
                445                 450                 455
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Ile Val Thr Val Gln Val Leu Pro Gln Cys Glu Cys Arg Cys Arg
460 465 470

Asp Gln Ser Arg Asp Arg Ser Leu Cys His Gly Lys Gly Phe Leu
475 480 485

Glu Cys Gly Ile Cys Arg Cys Asp Thr Gly Tyr Ile Gly Lys Asn
490 495 500

Cys Glu Cys Gln Thr Gln Gly Arg Ser Ser Gln Glu Leu Glu Gly
505 510 515

Ser Cys Arg Lys Asp Asn Asn Ser Ile Ile Cys Ser Gly Leu Gly
520 525 530

Asp Cys Val Cys Gly Gln Cys Leu Cys His Thr Ser Asp Val Pro
535 540 545

Gly Lys Leu Ile Tyr Gly Gln Tyr Cys Glu Cys Asp Thr Ile Asn
550 555 560

Cys Glu Arg Tyr Asn Gly Gln Val Cys Gly Gly Pro Gly Arg Gly
565 570 575

Leu Cys Phe Cys Gly Lys Cys Arg Cys His Pro Gly Phe Glu Gly
580 585 590

Ser Ala Cys Gln Cys Glu Arg Thr Thr Glu Gly Cys Leu Asn Pro
595 600 605

Arg Arg Val Glu Cys Ser Gly Arg Gly Arg Cys Arg Cys Asn Val
610 615 620

Cys Glu Cys His Ser Gly Tyr Gln Leu Pro Leu Cys Gln Glu Cys
625 630 635

Pro Gly Cys Pro Ser Pro Cys Gly Lys Tyr Ile Ser Cys Ala Glu
640 645 650

Cys Leu Lys Phe Glu Lys Gly Pro Phe Gly Lys Asn Cys Ser Ala
655 670 675

Ala Cys Pro Gly Leu Gln Leu Ser Asn Asn Pro Val Lys Gly Arg
680 685 690

Thr Cys Lys Glu Arg Asp Ser Glu Gly Cys Trp Val Ala Tyr Thr
695 670 675

Leu Glu Gln Gln Asp Gly Met Asp Arg Tyr Leu Ile Tyr Val Asp
680 685 690

Glu Ser Arg Glu Cys Val Ala Gly Pro Asn Ile Ala Ala Ile Val
695 700 705

Gly Gly Thr Val Ala Gly Ile Val Leu Ile Gly Ile Leu Leu Leu
710 715 720

Val Ile Trp Lys Ala Leu Ile His Leu Ser Asp Leu Arg Glu Tyr
725 730 735

Arg Arg Phe Glu Lys Glu Lys Leu Lys Ser Gln Trp Asn Asn Asp
740 745 750

Asn Pro Leu Phe Lys Ser Ala Thr Thr Thr Val Met Asn Pro Lys
755 760 765

Phe Ala Glu Ser

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Asp Val Asp Ser Asn Gly Ser Thr Asp
5

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Asp Val Asn Gly Asp Lys Leu Thr Asp
5

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Asp Leu Thr Met Asp Gly Leu Val Asp
5

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Asp Ser Asp Met Asn Asp Ala Tyr Leu
5

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Asn Ala Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu Lys Phe
5 10 15

Gly Asp Pro Leu Gly Tyr Glu Asp Val Ile Pro Glu Ala Asp Arg
20 25 30

Glu Gly Val

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Asp Gly Glu Lys Phe
5

Claims

1. A purified peptide comprising at least one extracellular region of a β2 integrin subunit capable of inhibiting a CD11/CD18 mediated immune response, said peptide lacking the transmembrane and cytoplasmic portions of said β2 integrin subunit, wherein said subunit is CD11b, CD11c or CD18.

2. The purified peptide of claim 1 wherein said β2 integrin subunit is CD11b.

3. The peptide of claim 3, said peptide comprising all or part of the A domain of CD11b.

4. The peptide of claim 3, said peptide comprising one of the following amino acid sequences:
   a. DIAFLIDGS (SEQ ID NO: 32),
   b. FRRMKEFVS (SEQ ID NO: 33),
   c. FKILVVITDGE (SEQ ID NO: 34),
   d. VIRYVIGVGDA (SEQ ID NO: 35),

5. The peptide of claim 3, said peptide comprising one of the following amino acid sequences:
   a. DGEKFGDPLG (SEQ ID NO: 36),
   b. YEDVIPEADR (SEQ ID NO: 37),
   c. DGEKFGDPLGYEDVIPEADR (SEQ ID NO: 17) or
   d. NAFKILVVITDGEKFGDPLGYEDVIPEADREGV (SEQ ID NO:50)
   e. DGEKF (SEQ ID NO: 51)

6. The peptide of claim 2 wherein said peptide comprises the following amino acid sequence: YYEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 38).

7. The peptide of claim 2 wherein said peptide comprises the following amino acid sequence: KSTRDRLR (SEQ ID NO: 15).

8. The peptide of claim 2, said peptide comprising one of the following amino acid sequences:

a. AYFGASLCSVDVDSNGSTDLVLIGAP (SEQ ID NO: 1),
b. GRFGAALTVLGDVNGDKLTDVAIGAP (SEQ ID NO: 2),
c. QYFGQSLSGGQDLTMDGLVDLTVGAQ (SEQ ID NO: 3),
d. YEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 4),
e. DIAFLIDGSGSIIPHDFRRMK (SEQ ID NO: 5),
f. RRMKEFVSTVMEQLKKSKTLF (SEQ ID NO: 6),
g. SLMQYSEEFRIHFTFKEFQNN (SEQ ID NO: 7),
h. PNPRSLVKPITQLLGRTHTATGIRK (SEQ ID NO: 8),
i. RKVVRELFNITNGARKNAFK (SEQ ID NO: 9),
j. FKILVVITDGEKFGDPLGYEDVIPEADR (SEQ ID NO: 10),
k. REGVIRYVIGVGDAFRSEKSR (SEQ ID NO: 11),
l. QELNTIASKPPRDHVFQVNNFE (SEQ ID NO: 12),
m. ALKTIQNQLREKIFAIEGT (SEQ ID NO: 13),
n. QTGSSSSFEHEMSQE (SEQ ID NO: 14),
o. FRSEKSRQELNTIASKPPRDHV (SEQ ID NO: 16),
p. KEFQNNPNPRSL (SEQ ID NO: 18),
q. GTQTGSSSSFEHEMSQEG (SEQ ID NO: 19),
r. SNLRQQPQKFPEALRGCPQEDSD (SEQ ID NO: 20),
s. RQNTGMWESNANVKGT (SEQ ID NO: 21),
t. TSGSGISPSHSQRIA (SEQ ID NO: 22),
u. NQRGSLYQCDYSTGSCEPIR (SEQ ID NO: 23),
v. PRGRARWQC (SEQ ID NO: 24),
w. KLSPRLQYFGQSLSGGQDLT (SEQ ID NO: 25),
x. QKSTRDRLREGQ (SEQ ID NO: 26),
y. SGRPHSRAVFNETKNSTRRQTQ (SEQ ID NO: 27),
z. CETLKLQLPNCIEDPV (SEQ ID NO: 28),
a'. FEKNCGNDNICQDDL (SEQ ID NO: 29),
b'. VRNDGEDSYRTQ (SEQ ID NO: 30),
c'. SYRKVSTLQNQRSQRS (SEQ ID NO: 31).

9. The peptide of claim 2, said peptide comprising one or more metal binding domains of CD11b.

10. The peptide of claim 9, said metal binding domains encompassing amino acids 358-412, 426-483, 487-553, and 554-614 of CD11b.

11. The peptide of claim 10, said peptide comprising one of the following sequences:

a. DVDSNGSTD (SEQ ID NO: 46),
b. DVNGDKLTD (SEQ ID NO: 47),
c. DLTMDGLVD (SEQ ID NO: 48), or
d. DSDMNDAYL (SEQ ID NO: 49)

12. The peptide of claim 1 or 2 wherein said peptide is soluble under physiological conditions.

13. A heterodimer comprising a first peptide and a second peptide, said first peptide comprising at least one extracellular region of a CD11 subunit and lacking the transmembrane and cytoplasmic portions of said CD11 subunit, said second peptide comprising at least one extracellular region of CD18 and lacking the transmembrane and cytoplasmic portions of CD18, said peptides being associated to form said heterodimer, said heterodimer being capable of inhibiting a CD11/CD18 mediated immune response.

14. The heterodimer of claim 13 wherein said CD11 subunit is CD11b.

15. The heterodimer of claim 13 wherein said CD11 subunit is CD11c.

16. The heterodimer of claim 14 wherein said heterodimer

is $CD11b^{1089}/CD18^{699}$

17. A method of controlling phagocyte-mediated tissue damage to a human patient, said method comprising administering a therapeutic composition to a patient said therapeutic composition comprising a physiologically acceptable carrier and either a peptide according to claim 1 or 2 or a heterodimer according to claim 13.

18. The method of claim 17 wherein said therapeutic composition is administered to control phagocyte-mediated tissue damage associated with ischemia-reperfussion.

19. The method of claim 17 wherein said therapeutic composition is administered to control phagocyte-mediated tissue damage to the heart muscle associated with reduced perfusion of heart tissue during acute cardiac insufficiency.

20. A method of producing a recombinant β2 integrin heterodimer, said method comprising:

(a) providing a recombinant cell encoding a CD11 peptide lacking both the transmembrane domain and the cytoplasmic domain and a CD18 peptide lacking both the transmembrane domain and the cytoplasmic domain;

(b) culturing said recombinant cell; and

(c) isolating said heterodimer from the culture supernatant.

21. The method of claim 20 wherein said recombinant β2 integrin heterodimer is soluble under physiological conditions.

22. The method of claim 20 wherein said CD11 peptide is a CD11b peptide.

23. The method of claim 20 wherein said soluble CD11 peptide is a recombinant CD11c peptide.

24. A monoclonal antibody which is raised to the peptide of claim 1 or claim 2 or the heterodimer of claim 13, said monoclonal antibody being capable of inhibiting a CD11/CD18 mediated immune response.

FIGURE 1

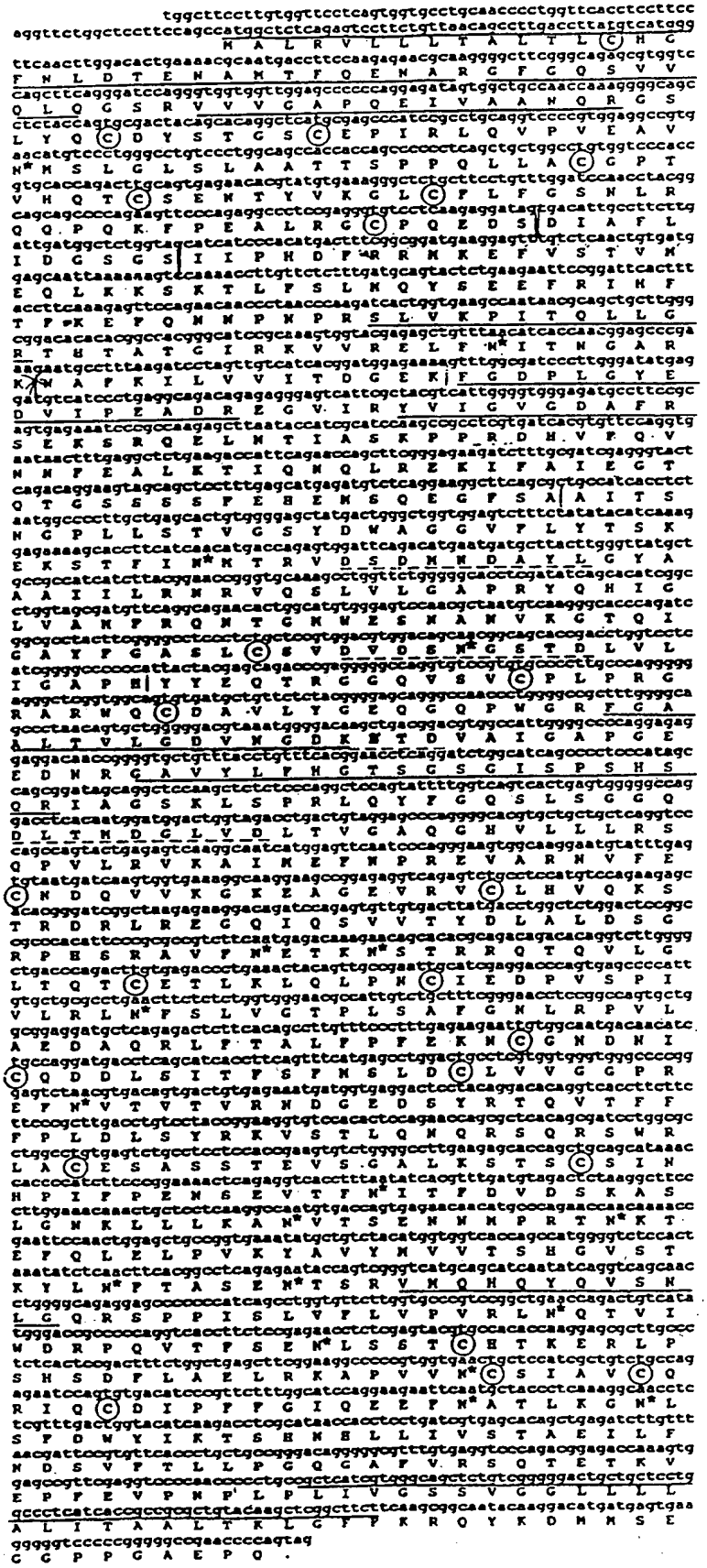

FIGURE 2

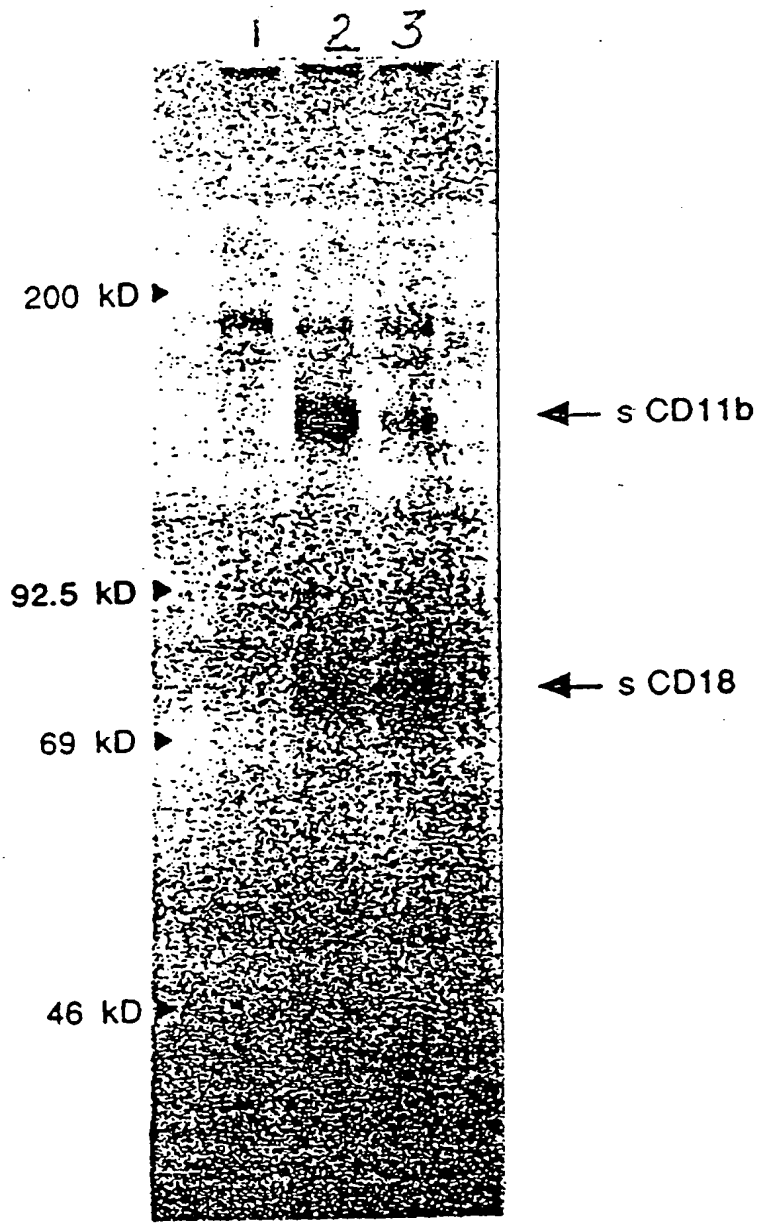

FIGURE 3

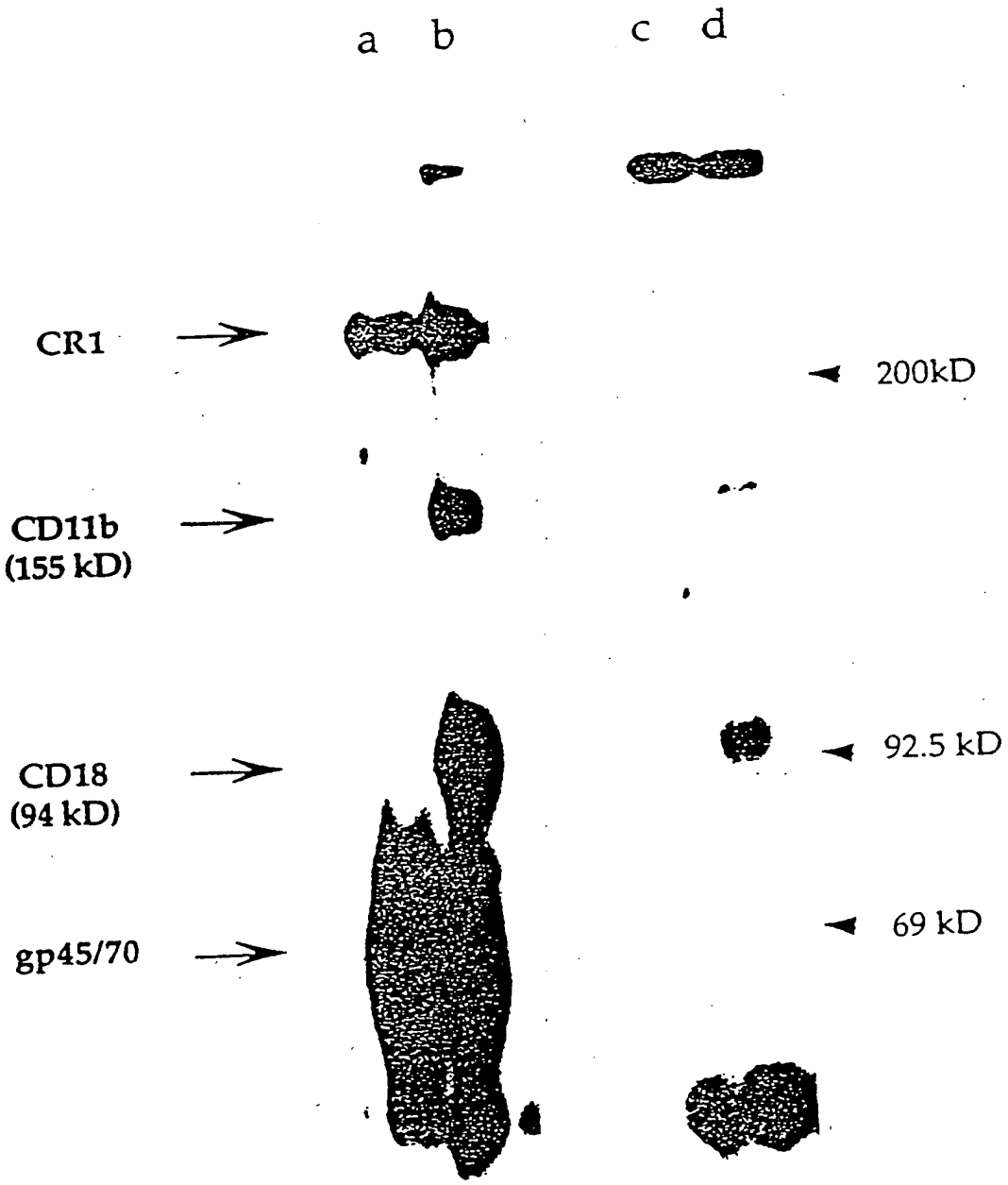

FIGURE 4

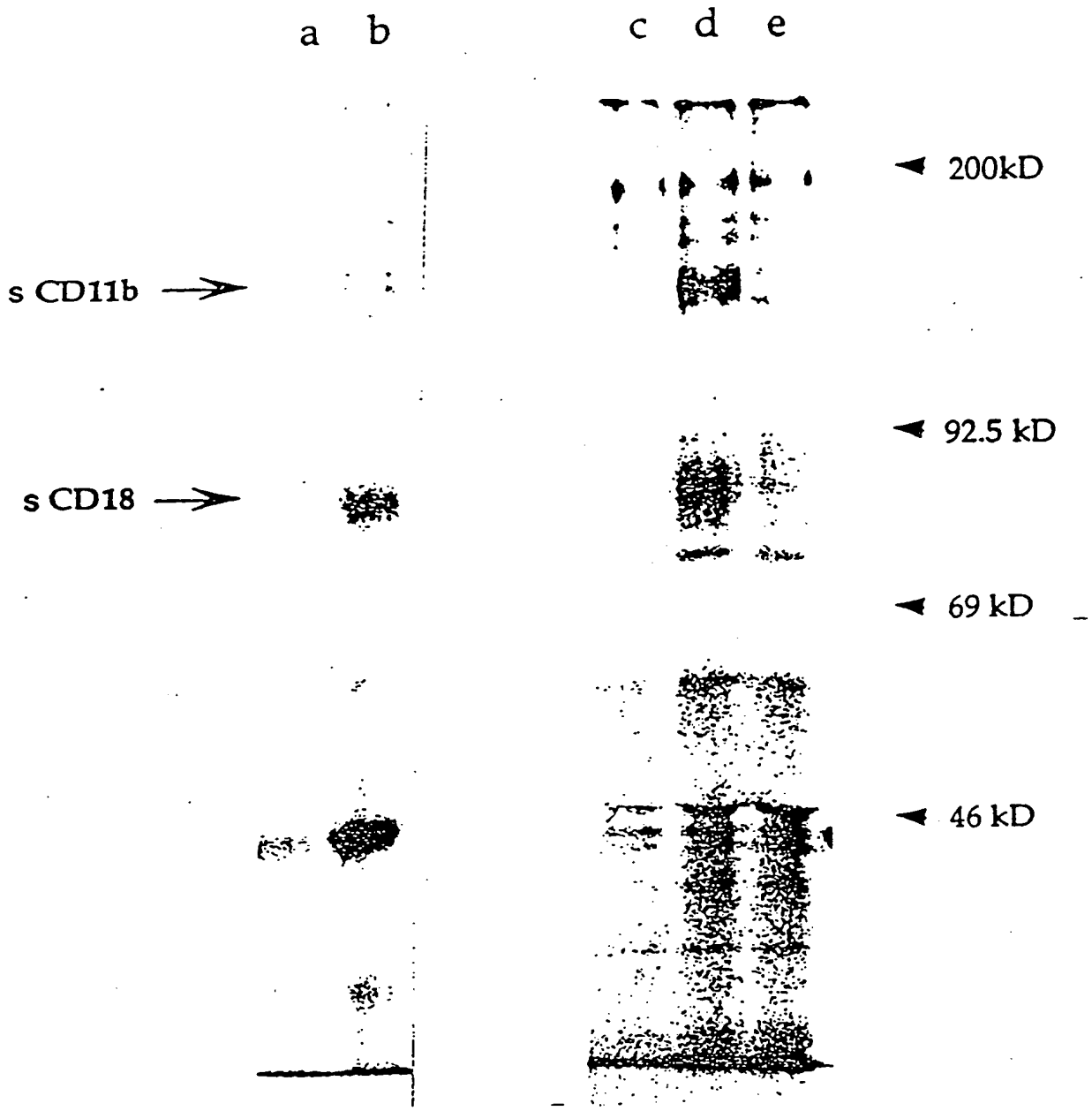

FIGURE 5

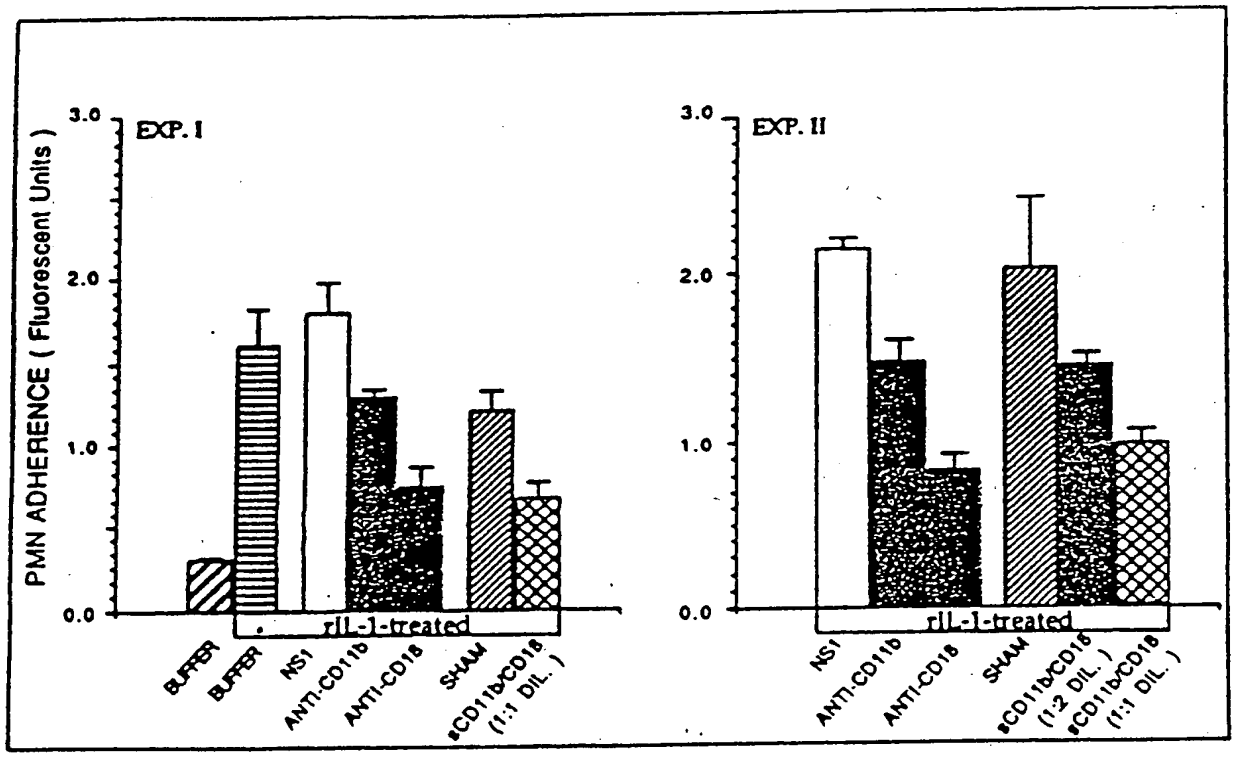
EXP. I
EXP. II
PMN ADHERENCE (Fluorescent Units)
3.0
2.0
1.0
0.0
rIL-1-treated
BUFFER
BUFFER
NS1
ANTI-CD11b
ANTI-CD18
SHAM
sCD11b/CD18 (1:1 DIL.)
sCD11b/CD18 (1:2 DIL.)

FIGURE 6

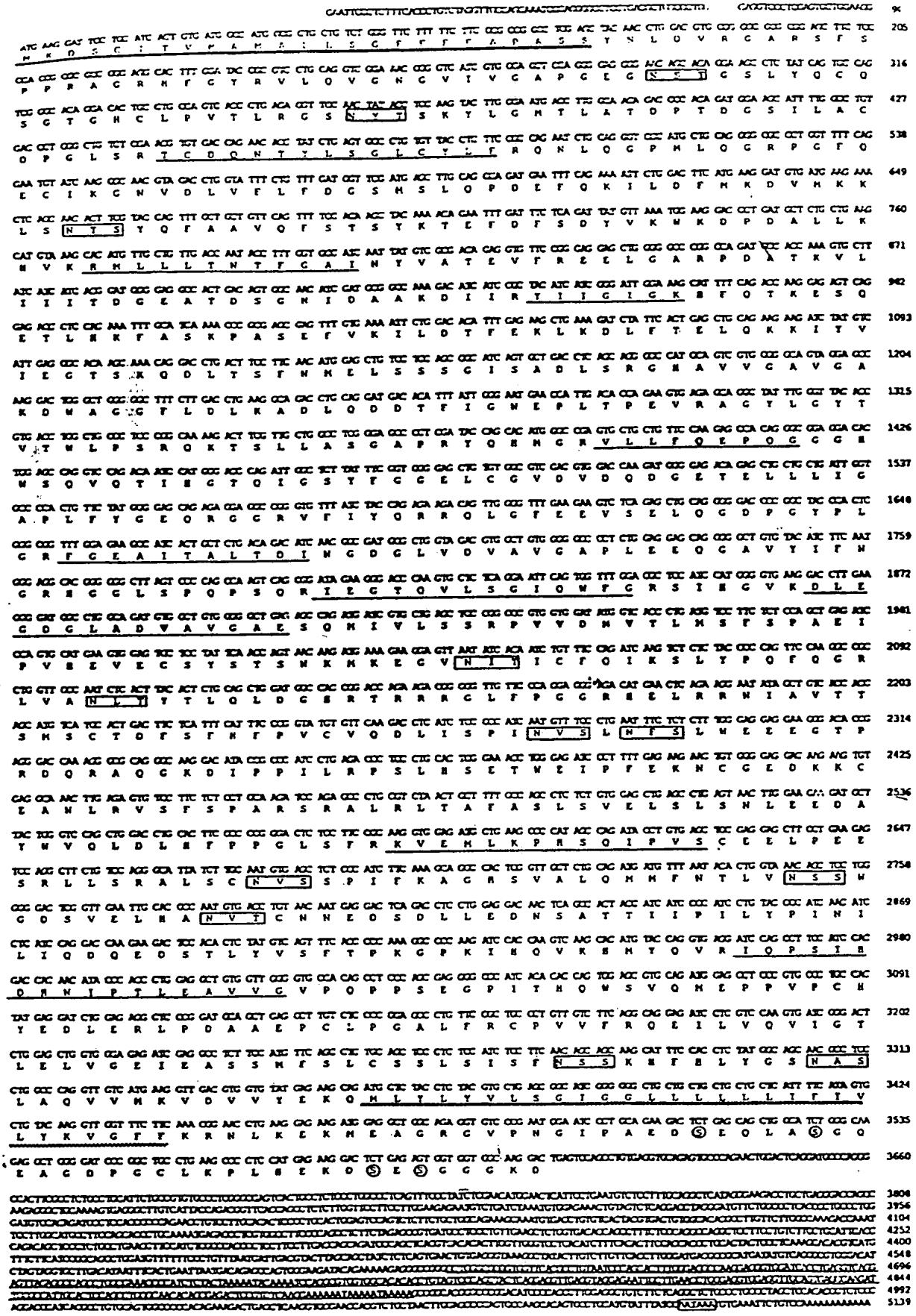

FIGURE 7

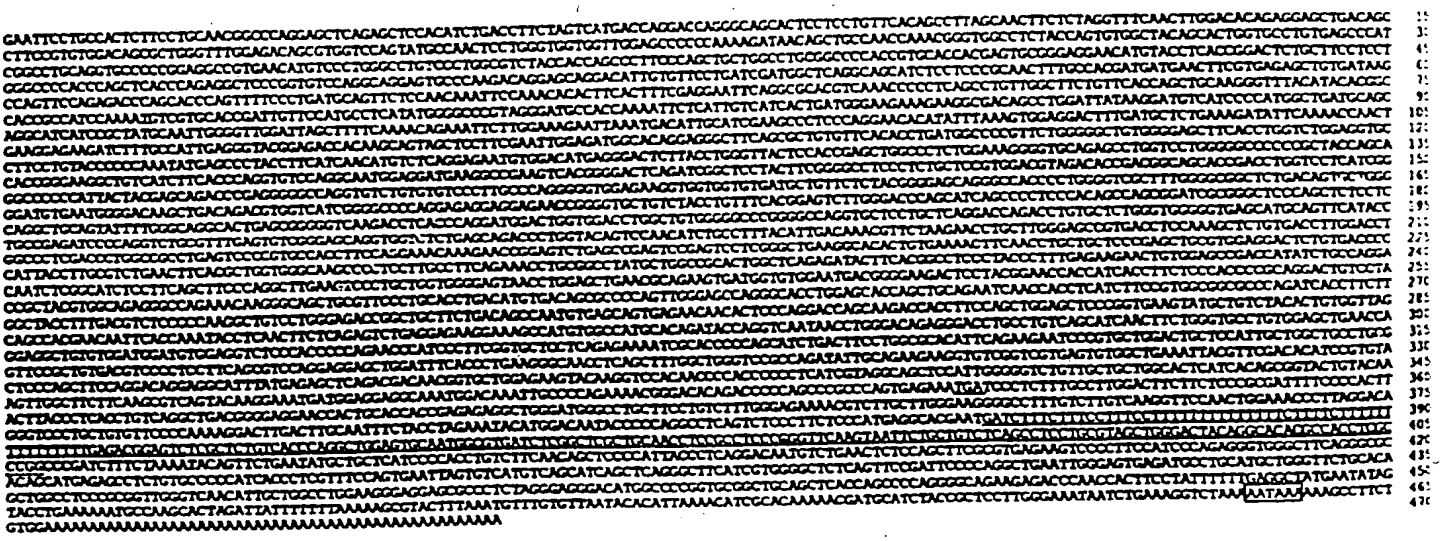

FIGURE 8


CTCCCCCTCGTCGCGCTGCTCTCCCTCCGCGTCGTCCTCTCTCTCAGCAGTCCACGAAGTTC 60
AAGCTCAGCAGCTGCCCCGCAATGCATCGAGTCCGCGCCCCGCCTGCACCTCGTCCCAGAAC 120
CTCAACTTCACAGCGCCCGCGGGATCCTGACTCCATTCGCCTCCGACACCCCGCCCACAGCTC 180
CTCATCAGCCGCTGTCCGCCTGACGACATCATGCACCCCACAACCCTCGCCTGAAACCCAC 240
CAACACCACAATCGCGCCCCAGAAGCAGCTGTCCCCACAAAAAGTGACGCTTTACCTGCCA 300
CCACCCCAGCCAGCAGCCGTTCAACGTGACCTTCCCCCCGCCCCAACCGCCTACCCCATCGAC 360
CTCTACTATCTGATGGACCTCTCCTACTCCATGCTTGATGACCTCAGGAATCTCAAGAAC 420
CTAGCTGCCGACCTGCTCCGCGCCCTCAACGACATCACCGACTCCGCCCCCATTGCCTTC 480
CGCTCCTTCGTCGACAAGACCGTCCTCCCCTTCGTCAACACGCACCCTCATAAGCTCCCA 540
AACCCATGCCCCAACAAGGAGAAAGAGTGCCACCCCCCCTTTCCCTTCAGCCAACGTCCTC 600
AACCTCACCAACAACTCCAACCAGTTTCAGACCGAGGTCGCGAAGCAGCTGATTTCCGGA 660
AACCTGCATGCACCCGAGGCTGGCCTGGACGCCATGATGCAGGTCGCCCCCTCCCCCGAG 720
CAAATCGCCTCCCCCAACGTCACCGCCCTCCTCGTCTTTGCCACTGATGACGCCTTCCAT 780
TTCCCGCGCCACCGAAAGCTGGCCCCCATCCTGACCCCCAACGACGCCCCCTCTCACCTC 840
CAGGACAACTTCTACAAGACGACCAACGAATTCCACTACCCATCGCTGCCCCACCTCGCC 900
CACAAGCTCGCCTGAAAACAACATCCACCCCATCTTCCCCGTGACCAGTACCATGCTGAAC 960
ACCTACGACAAACTCACCGAGATCATCCCCAAGTCAGCCGTCGCGCAGCTCTCTCAGCAC 1020
TCCAGCAATGTCGTCCATCTCATTAAGAATGCTTACAATAAACTCTCCTCCACGGTCTTC 1080
CTCGATCACAACGCCCTCCCCGACACCCTCAAACTCACCTACGACTCCTTCTGCAGCAAT 1140
GCACTCACGCACAGGAACCAGCCCACAGGTCACTGTCATCGCCGTCGACATCAATGTCCCG 1200
ATCACCTTCCACGTCAACGTCACGCCCACAGACTCCATCCAGCAGCAGTCCTTTGTCATC 1260
CCGCGCCTCGCCTTCACCGACATACTCACCGTCCACGTCCTTCCCCACTCTCACTCCCGC 1320
TCCCCGACCACAGCAGACACCCCACCCTCTGCCATCCCAACGCGTTCTTCGCACTCCCGC 1380
ATCTCCAGGTGTGACACTGGCTACATTCGGAAAAACTCTCACTCCCACACACACGCCCCG 1440
ACCAGCCACGAGCTCGAAGCAAGCTGCCCGAAGCACAACAACTCCATCATCTCCTCACCC 1500
CTCCCCCACTCTCTCTCCCCCCAGTCCCTCTCCCACACCAGCCACCTCCCCCCCAACCTC 1560
ATATACGCCCACTACTCCCAGTCTCACACCATCAACTCTCACCCCTACAACGCCCACCTC 1620
TCCCCCCCCCCCCGCACGCCCCTCTCCTTCTCCCCCAACTGCCCCTCCCACCCCCGCTTT 1680
CACCCCTCACCGTCCCAGTCCCACACGACCACTCACGCCTCCCTCAACCCCCCCCGTCTT 1740
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CTCCCTCTCTCCCACGCACTCCCCCCCCTCCCCCTCACCCTCTCCCAAGTACATCTCCTCC 1860
CCCCACTCCCTCAAGTTCGAAAACCCCCCCTTTCCCAACAACTCCACCCCCCCCTCTCCC 1920
CCCCTCCACCTCTCCAACACCCCGTCAAGCCCACCACCTCCAACCACACGGACTCACAC 1980
CCCTCCTCCCTCCCCTACACCCTCCACCACCACCACCCCATCCACCCCTACCTCATCTAT 2040
CTCCATCACACCCCACACTCTCTCCCCACCCCCCCAACATCCCCCCCATCCTCCCCCCCACC 2100
CTCCCACCCATCCTCCTCATCCCCATTCTCCTCCTCCTCATCTCCAACCCTCTCATCCCAC 2160
CTCACCCACCTCCCCCCACTACACCCCCTTTCACAACCACAACCTCAAGTCCCACTCCAAC 2220
AATCATAATCCCCTTTTCAACACCCCCACCACCACCCCTCATCAACCCCAACTTTCCTCAC 2280
ACTTACCACCA

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/04338

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 37/02, 39/00; C07K 7/06, 7/10, 13/00, 15/28, 7/08

U.S.: 530/324,325,326,327,328,350,387; 514/12,13,14,15

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	530/324,325,326,327,328,350,387; 514/12,13,14,15

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

Automated Patent Search, Chemical Abstract Service

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	Cell, Vol. 48, issued 27 February 1987, Kishimoto et al. "Cloning of the B Subunit of the Leukocyte Adhesion Proteins: Homology to an Extracellular Matrix Receptor Defines a Novel Supergene Family" pp.681-690, see Fig. 2 including legend.	1-23
Y	The EMBO Journal, vol. 7, No. 5, issued May 1988, Pytela, "Amino acid sequence of the Murine Mac-1 chair reveals homology with the integrin family and an additional domain related to Von Willebrand factor" pp. 1371-1378, see Fig. 2.	1-23

* Special categories of cited documents: [15]

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

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IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
08 August 1991	20 SEP 1991
International Searching Authority [1]	**Signature of Authorized Officer** [20]
ISA/US	Nina Ossanna, Ph.D.

Form PCT/ISA/210 (second sheet) (May 1986)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, [11] with indication, where appropriate, of the relevant passages [12]	Relevant to Claim No [13]
Y	The Journal of Biological Chemistry, vol. 263, No. 25, issued 05 September 1988, Corbi et al. "The Human Leukocyte Adhesion Glycoprotein Mac-1 (Complement Receptor Type 3, CD11b) Subunit" pp. 12403-12411. See Figs. 2 & 7.	1-23
X Y	The Journal of Immunology, vol. 137, No. 10, issued 15 November 1986, Dana et al. "Two Functional Domains in the Phagocyte Membrane Glycoprotein Mo1 Identified with Monoclonal Antibodies" pp. 3259-3263. See abstract.	24 1-23
Y	Proc. Natl. Acad. Sci. USA, vol. 83, issued September 1986, Mehra et al., "Efficient Mapping of Protein Antigenic Determinants" pp. 7013-7017. See entire article.	1-23

CORRECTED VERSION *

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 5 :
A61K 37/02, 39/00, C07K 7/06
C07K 7/10, 13/00, 15/28
C07K 7/08

A1

(11) International Publication Number: WO 91/19511

(43) International Publication Date: 26 December 1991 (26.12.91)

(21) International Application Number: PCT/US91/04338

(22) International Filing Date: 18 June 1991 (18.06.91)

(30) Priority data:
539,842 18 June 1990 (18.06.90) US
637,830 4 January 1991 (04.01.91) US

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(81) Designated States: AT (European patent), BE (European patent), CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FR (European patent), GB (European patent), GR (European patent), IT (European patent), JP, LU (European patent), NL (European patent), SE (European patent).

Published
With international search report.

(54) Title: CONTROLLING CELLULAR IMMUNE/INFLAMMATORY RESPONSES WITH β2 INTEGRINS

(57) Abstract

The invention features human CD11 recombinant or synthetic peptide capable of inhibiting a CD11/CD18-mediated immune response, a purified DNA encoding a human CD11b peptide, soluble heterodimeric molecules composed of a CD11 peptide and a CD18 peptide, and a method of controlling any phagocyte-mediated tissue damage such as that associated with reduced perfusion of heart tissue during acute cardiac insufficiency.

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+ Any designation of "SU" has effect in the Russian Federation. It is not yet known whether any such designation has effect in other States of the former Soviet Union.

CONTROLLING CELLULAR IMMUNE/INFLAMMATORY RESPONSES WITH β2 INTEGRINS

Background of the Invention

This invention, at least in part, was funded by a grant from the United States Government and the Government has certain rights in the invention.

This application is a continuation-in-part of my earlier, co-pending application USSN 539,842, filed June 18, 1990, which is in turn a continuation-in-part of my earlier application USSN 212,573, filed June 28, 1988, now abandoned, both of which are hereby incorporated by reference.

This invention relates to controlling cellular immune/inflammatory responses, particularly phagocyte-mediated tissue injury and inflammation.

Circulating phagocytic white blood cells are an important component of the cellular acute inflammatory response. It is believed that a number of important biological functions such as chemotaxis, immune adherence (homotypic cell adhesion or aggregation), adhesion to endothelium, phagocytosis, antibody-dependent cellular cytotoxicity, superoxide, and lysosomal enzyme release are mediated by a family of leukocyte surface glycoprotein adhesion receptors known as β_2 integrins or the CD11/CD18 complex. Arnaout et al., *Blood* 75:1037 (1990). Inherited deficiency of CD11/CD18 impairs leukocyte adhesion-dependent inflammatory functions and predisposes to life-threatening bacterial infections. Dana et al., *J. Clin. Invest.* 73:153 (1983); Arnaout et al., *J. Clin. Invest.* 74:1291 (1984).

The CD11/CD18 family consists of three heterodimeric surface glycoproteins, each with a distinct

α subunit (CD11a, CD11b or CD11c) non-covalently associated with a common β subunit (CD18). The divalent cations Ca^{+2} and Mg^{2+} are essential in the stabilization and function of the αβ (CD11/CD18) complex.

The β2 integrins are expressed only on leukocytes. While CD11a/CD18 (also known as LFA-1, TA-1) is expressed on all leukocytes, CD11b/CD18 and CD11c/CD18 (also known as LeuM5 or p150,95) are expressed primarily on monocytes, polymorphonuclear leukocytes, macrophages and natural killer cells CD11c/CD18 is also expressed on certain lymphocytes. Arnaout, *Blood* 75:1037 (1990).

CD11a/CD18, and not CD11b/CD18 or CD11c/CD18, is expressed on B- and T-lymphocytes; accordingly CD11a/CD18 plays a role in mitogen-, antigen-, and alloantigen-induced proliferation, T-cell-mediated cytotoxicity, lymphocyte aggregation, and Ig production. In contrast, all three CD11/CD18 molecules are important for monocyte/macrophage and granulocyte adhesion-dependent functions.

It is believed that CD11b/CD18 and CD11c/CD18 mediate enhanced adhesiveness of activated phagocytes through quantitative and qualitative changes in these proteins on the surface of activated cells. For example, in granulocytes, these proteins are translocated from intracellular storage pools present in secondary and tertiary granules. Arnaout et al., *J. Clin. Invest.* 74:1291 (1984); Arnaout et al., *New Eng. J. Med.* 312:457 (1985); Todd et al., *J. Clin. Invest.* 74:1280 (1984).

CD11b/CD18 is also known as complement receptor type 3 (CR3), Mo1, Mac-1 or MAM. See, Arnaout et al., *J. Clin. Invest.* 72:171 (1983), and references cited therein; Dana et al., *J. Immunol.* 137:3259 (1986); Wallis

et al., *J. Immunol.* 135:2323 (1985); Arnaout et al., *New Eng. J. Med.* 312:457 (1985); Dana et al., *J. Clin. Invest.* 73:153 (1984); and Beatty et al., *J. Immunol.* 131:2913 (1983). Like all β2 integrins, CD11b/CD18 consists of two non-covalently associated subunits. Kishimoto et al., *Cell* 48:681 (1987); Law et al., *EMBO J.* 6:915 (1987); Arnaout et al. *J. Clin. Invest.* 72:171 (1983). The α subunit of CD11b/CD18 has an apparent molecular mass of 155-165 kD and associates non-covalently with a β subunit, CD18, of apparent molecular mass 95 kD. Todd et al., *Hybridoma* 1:329 (1982).

Monoclonal antibodies have been used to identify at least two distinct functional domains of CD11b/CD18, one mediating homotypic and heterotypic adhesion and the other mediating binding to the complement C3 fragment (iC3b), the major C3 opsonin *in vivo*. Dana et al., *J. Immunol.* 137:3259 (1986).

Law et al., *EMBO J.* 6:915 (1987) and Kishimoto et al., *Cell* 48:681 (1987) disclose the nucleotide sequence of human CD18. Arnaout et al., *J. Cell Biol.* 106:2153 (1988); Corbi et al., *J. Biol. Chem.* 263:12403 (1988); and Hickstein et al., *Proc. Nat'l. Acad. Sci. USA* 86:275 (1989) disclose the nucleotide sequence of human CD11b. Larson et al., *J. Cell. Biol.* 108:703 (1989) disclose the nucleotide sequence of CD11a. Corbi et al., *EMBO J.* 6:4023 (1987) disclose the nucleotide sequence of CD11c.

Cosgrove et al.(*Proc. Nat'l. Acad. Sci. USA* 83:752, 1986) report a human genomic clone which produces "a molecule(s)" reactive with monoclonal antibodies to CD11b.

Sastre et al. (*Proc. Nat'l. Acad. Sci. USA* 83:5644, 1986) report a mouse genomic clone coding for an amino-terminal partial exon of murine CD11b. Pytela et

al., *EMBO J.* 7:1371 (1988) report a cDNA sequence of murine CD11b.

Simpson et al., *J. Clin. Invest.* 81:624 (1988) disclose that a monoclonal antibody (904) directed to an adhesion-promoting domain of CD11b (Dana et al., *J. Immunol.* 137:3259, 1986) reduces the extent of cardiac damage in dogs associated with myocardial infarction, presumably by limiting reperfusion injury. Vedder et al. (*J. Clin. Invest.* 81:939, 1988) similarly found that a monoclonal antibody directed against CD18 subunit of CD11b/CD18 reduced organ injury and improved survival from hemorrhagic shock in rabbits. In animal models, anti-CD11/CD18 antibodies have been shown to have protective effects in shock, frostbite, burns, cerebral edema, onset of diabetes mellitus (Hutchings et al., *Nature* 348:639, 1990) and transplant rejection. Reviewed in Carlos et al., *Immunol. Rev.* 114:5 (1990).

Summary of the Invention

The peptides and heterodimeric proteins of the invention are capable of antagonizing CD11/CD18 (β2 integrin) mediated immune response. CD11/CD18 mediated immune responses which it may be desirable to block include acute inflammatory functions mediated by neutrophils. The molecules of the invention are useful for treatment of ischemia reperfusion injury (e.g., in the heart, brain, skin, liver or gastrointestinal tract), burns, frostbite, acute arthritis, asthema, and adult respiratory distress syndrome. Peptides and heterodimeric proteins of the invention may also be useful for blocking intra-islet infiltration of macrophages associated with insulin-dependent diabetes mellitus.

The invention features a purified peptide which includes at least one extracellular region of a β2 integrin subunit capable of inhibiting a CD11/CD18 mediated immune response, the peptide lacks the transmembrane and cytoplasmic portions of the β2 integrin subunit. In a preferred embodiment the β2 integrin subunit is a human β2 integrin subunit; more preferably the β2 integrin subunit is CD11a, CD11b, CD11c or CD18; most preferably the β2 integrin subunit is CD11b. Preferably, the peptide includes all or part of the A domain of CD11b. More preferably the peptide includes one of the following sequences: DIAFLIDGS (SEQ ID NO: 32); FRRMKEFVS (SEQ ID NO: 33); FKILVVITDGE (SEQ ID NO: 34); VIRYVIGVGDA (SEQ ID NO: 35); DGEKFGDPLG (SEQ ID NO: 36); YEDVIPEADR (SEQ ID NO: 37); DGEKFGDPLGYEDVIPEADR (SEQ ID NO: 17); NAFKILVVITDGEKFGDPLGYEDVIPEADREGV (SEQ ID NO: 50); DGEKF (SEQ ID NO: 51). In preferred embodiments, the peptide includes the amino acid sequence YYEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 38); the peptide includes the amino acid sequence KSTRDRLR (SEQ ID NO: 15). Preferably, the peptide includes one of the following amino acid sequences:

AYFGASLCSVDVDSNGSTDLVLIGAP (SEQ ID NO: 1);
GRFGAALTVLGDVNGDKLTDVAIGAP (SEQ ID NO: 2);
QYFGQSLSGGQDLTMDGLVDLTVGAQ (SEQ ID NO: 3);
YEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 4);
DIAFLIDGSGSIIPHDFRRMK (SEQ ID NO: 5);
RRMKEFVSTVMEQLKKSKTLF (SEQ ID NO: 6);
SLMQYSEEFRIHFTFKEFQNN (SEQ ID NO: 7);
PNPRSLVKPITQLLGRTHTATGIRK (SEQ ID NO: 8);
RKVVRELFNITNGARKNAFK (SEQ ID NO: 9);
FKILVVITDGEKFGDPLGYEDVIPEADR (SEQ ID NO: 10);
REGVIRYVIGVGDAFRSEKSR (SEQ ID NO: 11);

QELNTIASKPPRDHVFQVNNFE (SEQ ID NO: 12); ALKTIQNQLREKIFAIEGT (SEQ ID NO: 13); QTGSSSSFEHEMSQE (SEQ ID NO: 14); FRSEKSRQELNTIASKPPRDHV (SEQ ID NO: 16); KEFQNNPNPRSL (SEQ ID NO: 18); GTQTGSSSSFEHEMSQEG (SEQ ID NO: 19); SNLRQQPQKFPEALRGCPQEDSD (SEQ ID NO: 20); RQNTGMWESNANVKGT (SEQ ID NO: 21); TSGSGISPSHSQRIA (SEQ ID NO: 22); NQRGSLYQCDYSTGSCEPIR (SEQ ID NO: 23); PRGRARWQC (SEQ ID NO: 24); KLSPRLQYFGQSLSGGQDLT (SEQ ID NO: 25); QKSTRDRLREGQ (SEQ ID NO: 26); SGRPHSRAVFNETKNSTRRQTQ (SEQ ID NO: 27); CETLKLQLPNCIEDPV (SEQ ID NO: 28); FEKNCGNDNICQDDL (SEQ ID NO: 29); VRNDGEDSYRTQ (SEQ ID NO: 30); SYRKVSTLQNQRSQRS (SEQ ID NO: 31).

Preferably, the peptide includes one or more metal binding domains of CD11b. More preferably, the metal binding domains encompass amino acids 358-412, 426-483, 487-553, and 554-614 of CD11b. Most preferably, the peptide includes one of the following sequences: DVDSNGSTD (SEQ ID NO: 46); DVNGDKLTD (SEQ ID NO: 47); DLTMDGLVD (SEQ ID NO: 48); DSDMNDAYL (SEQ ID NO: 49).

In a preferred embodiment, the peptides are soluble under physiological conditions.

In a related aspect, the invention features a heterodimer which includes a first peptide and a second peptide; the first peptide includes at least one extracellular region of a CD11 subunit and lacks the transmembrane and cytoplasmic portions of the CD11 subunit; the second peptide comprising at least one extracellular region of a CD18 subunit and lacks the transmembrane and cytoplasmic portions of the CD18 subunit; the first and second peptides are associated to form the heterodimer; and the heterodimer is capable of inhibiting a CD11/CD18 mediated immune response. In preferred embodiments, the CD11 subunit is: CD11a; CD11b;

CD11c. In a more preferred embodiment, the heterodimer is $CD11b^{1089}/CD18^{699}$.

In another aspect, the invention features a method of controlling phagocyte-mediated tissue damage to a human patient. The method includes administering a therapeutic composition to a patient; the therapeutic composition includes a physiologically acceptable carrier and a peptide or a heterodimer of the invention. More preferably, the method is used to control phagocyte-mediated tissue damage due to ischemia-reperfussion. Most preferably, the method is used to control phagocyte-mediated tissue damage to the heart muscle associated with reduced perfusion of heart tissue during acute cardiac insufficiency.

In another aspect, the invention features a method of producing a recombinant β2 integrin heterodimer. The method includes the steps of: (a) providing a recombinant cell encoding a CD11 peptide lacking both the transmembrane domain and the cytoplasmic domain and a CD18 peptide lacking both the transmembrane domain and the cytoplasmic domain; (b) culturing the recombinant cell; and (c) isolating the heterodimer from the culture supernatant. More preferably, the method is used to produce a soluble recombinant β2 integrin heterodimer. In preferred embodiments, the CD11 peptide of the heterodimer is a CD11a peptide; is a CD11b peptide; is a CD11c peptide.

In another aspect, the invention features a monoclonal antibody which is raised to a peptide or a heterodimer of the invention and which is capable of inhibiting a CD11/CD18 mediated immune response.

In another aspect, the features a human CD11b recombinant peptide.

"β2 integrins" include all leukocyte adhesion molecules which include a CD18 subunit. By the "A domain of CD11b" is meant the amino acid sequence corresponding to the sequence of CD11b from Cys^{128} to Glu^{321} or an amino acid sequence produced by introducing one or more conservative amino acid substitutions in an amino acid sequence corresponding to the sequence of CD11b from Cys^{128} to Glu^{321}. "CD11/CD18-mediated immune response" includes those CD11/CD18-related functions mentioned above: chemotaxis, immune adherence (homotypic cell adhesion or aggregation), adhesion to endothelium, phagocytosis, antibody-dependent or -independent cellular cytotoxicity, and superoxide and lysosomal enzyme release. Inhibition of these immune functions can be determined by one or more of the following inhibition assays as described in greater detail below: iC3b binding, cell-cell aggregation, phagocytosis, adhesion to endothelium, and chemotaxis. As used herein, a human CD11b recombinant peptide is a chain of amino acids derived from recombinant CD11b-encoding cDNA, or the corresponding synthetic DNA. "$CD11^{1089}/CD^{18699}$" is a heterodimer which comprises amino acids 1-1089 of human CD11 and amino acids 1-699 of CD18.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

The drawings will first briefly be described.

Drawings

Figure 1 is the cDNA sequence and deduced amino acid sequence of the open reading frame of human CD11b from Arnaout et al., *J. Cell. Biol.* 106:2153 (1988).

Figure 2 is a representation of the results of an immunoprecipitation assay.

Figure 3 is a representation of the results of an immunoprecipitation assay.

Figure 4 is a representation of the results of an immunoprecipitation assay.

Figure 5 is a graph of the effect of various proteins and antibodies on neutrophil adhesion to endothelium.

Figure 6 is the cDNA sequence and deduced amino acid sequence of human CD11a from Larson et al., *J. Cell. Biol.* 108:703 (1989).

Figure 7 is the cDNA sequence and deduced amino acid sequence of human CD11c from Corbi et al., *EMBO J.* 6:4023 (1987).

Figure 8 is the cDNA sequence of human CD18 from Law et al., *EMBO J.* 6:915 (1987).

Peptides

As described in greater detail elsewhere, each member of the β2 integrin family is a heterodimer consisting of two subunits: a CD11 subunit (with at least three variants designated CD11a, CD11b, and CD11c) and a CD18 subunit. Each subunit includes a transmembrane anchor which connects a cytoplasmic segment to an extracellular segment. The two subunits interact to form a functional heterodimer. As described in greater detail below, the extracellular segments of the β2 integrin

subunits contain various functional domains which are the focus of the invention.

Without wishing to bind myself to a particular theory, it appears that the peptides of the invention antagonize CD11/CD18-mediated immune responses by competitively inhibiting binding of leukocytes bearing a member of the β_2 integrin family to the respective binding partners of that family. Specifically, the peptides of the invention include an immune-response inhibiting extracellular segment of any one of the $\beta 2$ integrin subunits --CD11a, CD11b, CD11c, CD18-- or a heterodimer composed of a portion of an α (CD11a, CD11b, or CD11c) subunit together with a portion of a β subunit (CD18). Candidate $\beta 2$ integrin subunits can be evaluated for their ability to antagonize CD11/CD18-mediated immune responses by any of several techniques. For example, subunits may be tested for their ability to interfere with neutrophil adhesion to endothelial cells using an assay described in detail below. Specific regions of the $\beta 2$ integrin subunits can be evaluated in a similar manner. Any extracellular region of a $\beta 2$ integrin subunit may be screened for its ability to interfere with CD11/CD18 mediated immune response. Regions of CD11 whose sequences are conserved between two or more subunits are preferred candidates for antagonizing CD11/CD18 - mediated immune response. For example, the A domain (corresponding to Cys^{128} to Glu^{321} of CD11b) is conserved between CD11a, CD11b, and CD11c. The A domain is 64% identical in CD11b and CD11c and 36% homologous between these two subunits and CD11a. This domain is also homologous to a conserved domain in other proteins involved in adhesive interactions including von Willebrand's factor, cartilage matrix protein, VLA2, and

the complement C3b/C4b - binding proteins C2 and factor B. The extracellular portions of CD11a, CD11b and CD11c include seven homologous tandem repeats of approximately 60 amino acids. These repeats are also conserved in the α subunits of other integrin subfamilies (e.g., fibronectin receptor). Arnaout et al., *Blood* 75:1037 (1990).

Regions of CD18 which are conserved among β intergrin subunits (i.e., the β subunits of β1, β2 and β3 integrins) are also good candidates for regions capable of interfering with CD11/CD18 - mediated immune response. For example, CD18 has four tandem repeats of an eight-cysteine motif. This cysteine-rich region is conserved among β subunits. Just amino terminal to this cysteine rich region is another conserved region, 247 amino acids long, which is conserved in several integrin β subunits.

Described in detail below are techniques for generating CD11b peptides and heterodimers. The same techniques may be used to generate CD11a, CD11c, and CD18 peptides as well as CD11a/CD18 and CD11c/CD18 heterodimers. Fig. 6 depicts the cDNA sequence of human CD11a (SEQ ID NO: 39); Fig. 7 depicts the cDNA sequence of human CD11c (SEQ ID NO:); Fig. 8 depicts the cDNA sequence of CD18 (SEQ ID NO: 41).

DNA molecules encoding all or part of CD11a, CD11b, CD11c or CD18 can be obtained by means of polymerase chain reaction amplification. In this technique two short DNA primers are used to generate multiple copies of a DNA fragment of interest from cells known to harbor the mRNA of produced by the gene of interest. This technique is described in detail by Frohman et al., *Proc. Nat'l Acad Sci. USA* 85:8998 (1988). Polymerase chain reaction methods are generally described

by Mullis et al. (U.S. Patent Nos. 4,683,195 and 4,683,202).

For example, to clone a portion of CD11a, the known sequence of CD11a is used to design two DNA primers which will hybridize to opposite strands outside (or just within) the region of interest. The primers must be oriented so that when they are extended by DNA polymerase, extension proceeds into the region of interest. To generate the CD11a DNA, poyA RNA is isolated from cells expressing CD11a. A first primer and reverse transcriptase are used to generate a cDNA form the mRNA. A seond primer is added; and *Taq* DNA polymerase is used to amplify the cDNA genrated in the previous step. Alternatively, the known sequences of CD11a, CD11b, CD11c and CD18 can be used to design highly specific probes for identifying cDNA clones harboring the DNA of interest. A cDNA library suitable for isolation of CD11a, CD11b, and CD11c DNA can be generated using phorbol ester-induced HL-60 cells (ATCC Accession No. CCL 240) as described by Corbi et al. (*EMBO J.* 6:4023, 1987) and Arnaout et al., *Proc. Nat'l Acad Sci. USA* 85:2776, 1988); CD18 DNA can be isolated from a library generated using U937 cells (ATCC Accession No. CRL 1593) as described by Law et al. (*EMBO J.* 6:915, 1987). These cell lines are also suitable for generating cDNA by polymerase chain reaction amplification of mRNA as sescribed above.

Heterodimers comprised of part of CD11c and CD18 can be produced as described below for CD11b/CD18 by changing a codon amino terminal to the transmembrane region (e.g. Pro^{1086}) to a stop codon. Heterodimers comprised of part of CD11a can be produced by changing a codon amino terminal to the transmembrane region (e.g.,

Lys^{1087}) to a stop codon. DNA encoding the truncated CD11 subunit is then introduced into cells along with DNA encoding a similarly truncated CD18 molecule (described below). These cells are then used as a source of heterodimer.

Isolation of a Human CD11b cDNA clone.

A 378 base pair (bp) cDNA clone encoding guinea pig CD11b was used as a probe to isolate three additional cDNA clones from a human monocyte/lymphocyte cDNA library as described in Arnaout et al., *Proc. Nat'l. Acad. Sci. USA* 85:2776 (1988); together these three clones contain the 3,048 nucleotide sequence encoding the CD11b gene shown in Fig. 1 (SEQ ID NO: 40). Arnaout et al., *J. Cell. Biol.* 106:2153 (1988).

In order to express CD11b, a mammalian expression vector was constructed by assembling the above-described three cDNA clones. Appropriate restriction enzyme sites within the CD11b gene can be chosen to assemble the cDNA inserts so that they are in the same translation reading frame. Arnaout et al., *J. Clin. Invest.* 85:977 (1990). A suitable basic expression vector can be used as a vehicle for the 3,048 bp complete cDNA fragment encoding the human CD11b peptide; the recombinant cDNA can be expressed by transfection into, e.g., COS-1 cells, according to conventional techniques, e.g., the techniques generally described by Aruffo et al., *Proc. Nat'l. Acad. Sci. USA* 84:8573 (1987) or expressed in *E. coli* using standard techniques. Smith et al., *Gene* 67:31 (1988).

Isolation of CD11b Peptide from Mammalian Cells

The CD11b protein can be purified from the lysate of transfected COS-1 cells, using affinity chromatography and lentil-lectin Sepharose and available anti-CD11b

monoclonal antibody as described by Pierce et al. (1986) *supra* and Arnaout et al., *Meth. Enzymol.* 150:602 (1987).

If the desired CD11b peptide is shorter than the entire protein, DNA encoding the desired peptide can be expressed in the same mammalian expression vector described above using the selected DNA fragment and the appropriate restriction enzyme site, as outlined above. The selected DNA fragment may be isolated according to conventional techniques from one of the CD11b cDNA clones or may be synthesized by standard polymerase chain reaction amplification, as described above. See also Saiki et al., (*Science* 239:487, 1988).

Characterization of the CD11b Polypeptide

The coding sequence of the complete CD11b protein is preceded by a single translation initiation methionine. The translation product of the single open reading frame begins with a 16-amino acid hydrophobic peptide representing a leader sequence, followed by the NH_2-terminal phenylalanine residue. The translation product also contained all eight tryptic peptides isolated from the purified antigen, the amino-terminal peptide, and an amino acid hydrophobic domain representing a potential transmembrane region, and a short 19-amino acid carboxy-terminal cytoplasmic domain (Fig. 1 illustrates the amino acid sequence of CD11b; SEQ ID NO: 43). The coding region of the 155-165 kD CD11b (1,136 amino acids) is eight amino acids shorter than the 130-150 kD alpha subunit of CD11c/CD18 (1,144 amino acids). The cytoplasmic region of CD11b contains one serine residue that could serve as a potential phosphorylation site. The cytoplasmic region is also relatively rich in acidic residues and in proline (Fig.

1). Since CD11b/CD18 is involved in the process of phagocytosis and is also targeted to intracellular storage pools, these residues are candidates for mediating these functions. The long extracytoplasmic amino-terminal region contains three or four metal-binding domains (outlined by broken lines in Fig. 1) that are similar to Ca^{2+}-binding sites found in other integrins. Each metal binding site may be composed of two noncontiguous peptide segments and may be found in the four internal tandem repeats formed by amino acid residues 358-412, 426-483, 487-553, and 554-614. The portion of the extracytoplasmic domain between Tyr^{465} and Val^{492} is homologous to the fibronectin-like collagen binding domain and IL-2-receptor. The extracytoplasmic region also contains an additional unique 187-200 amino acid domain, the A domain, between Cys^{128} to Glu^{321}, which is not present in the homologous (α) subunits of fibronectin, vitronectin, or platelet IIb/IIIa receptors. This sequence is present in the highly homologous CD11c protein (α of p150,95) with 64% of the amino acids identical and 34% representing conserved substitutions. Arnaout et al., *J. Cell Biol.* 106:2153, 1988; Arnaout et al. *Blood* 75:1037 (1990). It is known that both CD11b/CD18 and CD11c/CD18 have a binding site for complement fragment C3 and this unique region may be involved in C3 binding. This region of CD11b also has significant homology (17.1% identity and 52.9% conserved substitutions) to the collagen/heparin/platelet GpI binding regions of the mature von Willebrand factor (domains A1-A3). The A domain is also homologous to a region in CD11a. Larson et al., *J. Cell Biol.* 108:703 (1989). The A domain is also referred to as the L domain or the I domain. Larson et al., *supra* (1988); Corbi et

al., *J. Biol. Chem.* 263:12,403 (1988).

CD11b Peptides

The following peptides can be used to inhibit CD11b/CD18 activity: a) peptides identical to the above-described A domain of CD11b, or a portion thereof, e.g., DIAFLIDGS (SEQ ID NO:32), FRRMKEFVS (SEQ ID NO:33), FKILVVITDGE (SEQ ID NO:34), DGEKFGDPLGYEDVIPEADR (SEQ ID NO:17), or VIRYVIGVGDA SEQ ID NO:35); b) peptides identical to the above-described fibronectin-like collagen binding domain, or a portion thereof, e.g., YYEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO:38); c) peptides identical to one or more of the four metal binding regions of CD11b, or a portion thereof, e.g., DVDSNGSTD (SEQ ID NO:46), DVNGDKLTD (SEQ ID NO:47), DLTMDGLVD (SEQ ID NO:48), DSDMNDAYL (SEQ ID NO:49); d) peptides substantially identical to the complete CD11b; or e) other CD11b domains, e.g. KSTRDRLR (SEQ ID NO:15).

Also of interest is a recombinant peptide which includes part of the A domain, e.g, NAFKILVVITDGEKFGDPLGYEDVIPEADREGV (SEQ ID NO: 50). The A domain binds iC3b, gelatin, and fibrinogen and binding is disrupted by EDTA. The A domain also binds both Ca^{2+} and Mg^{2+}. This result unexpected since the A doamin lies outside of the region of CD11b previously predicted (Arnaout et al., *J. Cell Biol.* 106:2153, 1988; Corbi et al., *J. Biol. Chem.* 25:12403, 1988) to contain metal binding sites.

Heterodimers

It is advantageous to administer the heterodimer formed by the CD11b and CD18 proteins. Expression of CD11b is described elsewhere in this application. Expression of CD18 has been reported by others. Law et al. *Embo, J.* 6:915 (1987); Kishimoto et al. *Cell* 48:681

(1987). The strategies described above or in those reports can be used to obtain CD18 to make such a heterodimer. Preferred heterodimers are soluble under physiological conditions. The heterodimer described below is generated by changing the codon for Leu^{1090} in CD11b (SEQ ID NO: 40) to a stop codon and the codon for Asn^{700} of CD18 (SEQ ID NO: 41) to a stop codon. Other potentially soluble heterodimers can be generated by introducing a stop codon at positions amino terminal to those described below.

Generation of Soluble Heterodimers

A soluble form of a CD11b/CD18 heterodimer was produced in COS cells. To produce this molecule the codons for Leu^{1090} and Asn^{700} located at the predicted extracellular boundaries of CD11b and CD18 respectively, were replaced with in-frame translational stop codons using oligonucleotide-directed gapped-duplex mutagenesis of the wild-type cDNAs (described below).

To determine if COS cells can express a soluble form of CD11b/CD18, COS cells were co-transfected with cDNA encoding the truncated forms of CD11b ($CD11b^{1089}$) and CD18 ($CD11^{699}$). Secreted proteins were analyzed by immunoprecipitation and SDS-PAGE. The results of this analysis are presented in Fig. 2.

Briefly, COS cells were transfected as previously described (Arnaout et al., *J. Clin. Invest.* 85:977, 1990). 7×10^6 transfected cells were labeled overnight with 0.1 mCi of ^{35}S methionine, and the harvested supernatants were used for immunoprecipitation with NS1, a non-reactive monoclonal antibody (mAb) (lane 1); 44a, an anti-CD11b mAb (lane 2); or TS18, an anti-CD18 mAb (lane 3). Immunoprecipitation and antibodies as described by Arnaout et al., *J. Cell. Physiol.* 137:305

(1988); Trowbridge et al., *J. Exp. Med.* 154:1517 (1981); and Sanchez-Madrid et al., *J. Exp. Med.* 158:1785 (1983).

As shown in Fig. 2, both $CD11b^{1089}$ and $CD18^{699}$ were immunoprecipitated from supernatants of cells transfected with DNA encoding the truncated subunits. The secreted $CD11b^{1089}$ had an apparent molecular weight of 149 kD; the secreted $CD18^{699}$ had an apparent molecular weight of 84 kD (compared to 155 kD and 94 kD respectively for the wild-type subunits). Arnaout et al., *New Engl. J. Med.* 312:457 (1985); Dierner et al., *J. Immunol.* 135:537 (1985); Arnaout et al., *J. Clin. Invest.* 72:171 (1983); Klebanoff et al., *J. Immunol.* 134:1153 (1985). That mAbs directed against either the CD11b or CD18 immunoprecipitated both truncated forms, indicates that the secreted subunits are expressed as an $CD11b^{1089}/CD18^{699}$ complex and that neither the cytoplasmic nor the transmembrane region of the subunits are necessary for heterodimer formation. These mAbs did not precipitate receptor subunits from the supernatants of mock-transfected cells. Arrowheads at left indicate the positions of molecular weight size markers: myosin (200kD), phosphorylase b (92.5 kD), bovine serum albumin (69 kD), and ovalbumin (46 kD). Arrows at right indicate the expected positions of $CD11b^{1089}$ and $CD18^{699}$.

$CD11b^{1089}/CD18^{699}$ was next tested for its ability to bind iC3b (the receptor bound by wild-type CD11b/CD18). Briefly, COS cells were transfected $CD11b^{1089}$ and $CD18^{699}$ cDNA as described above. Cells were labeled with ^{35}S-methionine as described by Dana et al., *J. Clin. Invest.* 79:1010 (1987). Supernatants from both co-transfected COS cells (7×10^6 cells) and mock-transfected COS cells (7×10^6 cells) were concentrated to one ml using collodion bags (10,000 MW cut off). 100

μl of the concentrated supernatant were used for immunoprecipitation, and the rest of the supernatant was incubated with C3b-sepharose or iC3b-sepharose. C3b-sepharose and iC3b-sepharose was washed, eluted with 0.4 M NaCl and the eluted proteins were analyzed by SDS-PAGE and autoradiography. Binding of wild-type, membrane-bound CD11b/CD18 to iC3b-sepharose or C3b-sepharose was performed as described by Arnaout et al., (*In Methods in Enzymology*, DiSabato, Ed., Acad. Press Inc., Fl., 1987) using the detergent soluble fraction from 1×10^8 ^{125}I-surface-labelled neutrophils.

Fig. 3 illustrates the results of SDS-PAGE analysis of neutrophil-derived ^{125}I-surface-labeled glycoproteins eluted from C3b-sepharose and iC3b-sepharose. Eluants from C3b-sepharose (lane a) contained complement receptor type 1 (250kD) and the C3-binding regulatory protein gp45/70 (45-70 kD). Eluants from iC3b-sepharose (lane b) contained two additional proteins at 155 kD, 94 kD, representing wild-type CD11b and CD18. CD11b/CD18 was immunoprecipitated with 44a mAb (an anti-CD11b mAb) from material eluted from iC3b-sepharose (lane d), but not from material eluted from C3b-sepharose (lane c), confirming previous results. Malhorta et al., *Eur. J. Immunol.* 16:177, (1986). The arrowheads at right indicate the positions of molecular weight standards: myosin (200 kD), phosphorylase b (92.5 kD), and bovine serum albumin (69 kD). The arrows at left indicate the expected position of CR1, CD11b, CD18 and gp45/70.

Fig. 4 shows the results of SDS-PAGE analysis of CD11b^{1089}/CD18^{699} heterodimer binding to iC3b. An anti-CD11b mAb (44a) was used to immunoprecipitate proteins from culture supernatants of mock-transfected COS cells (lane a), and from COS cells co-transfected with CD11b^{1089}

and $CD18^{699}$ cDNAs (lane b). No specific radiolabeled material was present in eluant of iC3b-sepharose exposed to culture supernatant of mock-transfected COS cells (lane c). $CD11b^{1089}/CD18^{699}$ was eluted from iC3b-sepharose (lane d), but not from C3b-sepharose (lane e) exposed to culture supernatant of co-transfected cells. Arrowheads at right indicate the positions of molecular weight standard standards (as in Fig. 2). Arrows at left indicate the expected positions of $CD11b^{1089}$ and $CD18^{699}$. Similar results were seen with supernatants from two other transfections.

The ability of $CD11b^{1089}/CD18^{699}$ to inhibit binding of human neutrophils to inflamed endothelium was examined and compared to the inhibition induced by anti-CD11b mAb and anti-CD18 mAb. Adherence of purified human neutrophils to confluent monolayers of human umbilical vein endothelial cells (HUVE) pre-treated with recombinant IL-1 (10 units/ml for 4 hours at 37°C) was measured as described by Arnaout et al., (*J. Cell. Physiol.* 137:305, 1988) with the following modifications. Neutrophils were labeled with carboxyfluorescein (CF, Molecular Probes, Eugene, OR) by incubating 4×10^6 cells with 30 μg of CF in one ml of Tris-buffered saline for 10 minutes on ice, followed by three washes. HUVE were pre-incubated for 10 minutes at 37°C with supernatants of COS cells co-transfected with $CD11b^{1089}$ and $CD18^{699}$ cDNA supernatants, or for 5 minutes at room temperature with the non-reactive monoclonal antibody NS1, 44a (anti-CD11b) or TS18 (anti-CD18) ascites (1:100 dilution). Labeled neutrophils were then added and incubation was continued for an additional 10 minutes. The plates HUVE were washed twice, and adherent neutrophils were harvested by washing with 0.1% SDS and 0.1N NaOH.

Relative numbers of neutrophils were measured (at Exc., 490 nm; Em, 300nm) using a Fluorometer (SLM 8000, SLM Aminco, Urbana, IL). All assays were done in triplicate. Labels along the horizontal axis indicate the molecule added to HUVE. 'Buffer' indicates that no antibodies were added. 'Sham' indicates that supernatant from mock transfected cells was added.

As shown in Fig. 5, culture supernatants containing $CD11b^{1089}/CD18^{699}$ (approximately 10-50 ng/ml) were found to be at least as effective in blocking neutrophil adhesion to rIL-1-induced endothelium as monoclonal antibodies directed against CD11b or CD18. $CD11b^{1089}/CD18^{699}$ was more effective than 44a mAb (an anti-CD11b mAb) in inhibiting adhesion to rIL-1-activated endothelium and comparable to inhibition seen using TS18 mAb (an anti-CD18 mAb), suggesting the presence of multiple functional sites on $CD11b^{1089}$ and/or the possibility that CD18 (like other β integrins) contains a recognition site(s) for interacting with ligand(s) expressed on endothelium.

Generation of Truncated CD11b and CD18 PAT-X plasmid containing the partial CD18 cDNA clone J19 (Law et al. *supra*, 1987) was linearized with HindIII or digested with NcoI (to generate a 1331 bp gap). These two plasmids were mixed with an excess of the synthetic and 5'-end phosphorylated 18-mer (5'-aggccccTaGatcgccgc) containing desired nucleotide mutations (caps). The mixture was denatured by boiling and renatured by stepwise cooling. Reannealed DNA (containing single-stranded region to which the mutant 18-mer is hybridized) was primer extended to fill the gap, and used to transform *E. coli* strain BMH 71-18 mutL. Arnaout et al., *J. Clin. Invest.* 85:977 (1990). Plasmids containing the mutation were

identified by differential hybridization with ^{32}P-labeled wild-type- or mutant 18-mers and DNA used to transform *E. coli* JM109. Positive colonies were identified following rehybridization, sequenced to verify the mutation, then used to replace the corresponding fragment in wild-type full length CD18 cDNA cloned in πH3M expression vector. Arnaout et al., *J. Clin. Invest.* 85:977 (1990). A stop codon was similarly introduced in CD11b. Blue Script (Stratagene, La Jolla, CA) plasmid vector containing the full coding region of membrane-bound CD11b was used. A mixture of KpnI-linearized and gapped (by removing a SmaI fragment, 1048 bp long) CD11b cDNAs were mixed with an excess of the synthetic mutant 18-mer (5'-caaccccTAgccgctcat). Mutant plasmid was produced and isolated as detailed above.

Monoclonal Antibodies

Monoclonal antibodies directed against CD11 or CD18 can be used to antagonize CD11/CD18-mediated immune response. Useful monoclonal antibodies can be generated by using a peptide of the invention as an immunogen. For example, monoclonal antibodies can be raised against the A domain of CD11b, CD11a or CD11c.

Anti-CD11b monoclonal antibodies which inhibit iC3b binding (mAb 903), neutrophil adhesive interactions, e.g., aggregation and chemotaxis, (mAb 904), or both activities (mAb44a) have been identified. Other monoclonal antibodies (OKM-1, which inhibits fibrinogen binding, and OKM9) have also been mapped to this region. Dana et al., *J. Immunol.* 137:3259 (1986). These monoclonal antibodies recognize epitopes in the A domain of CD11b. Dana et al., *JASON* 1:549 (1990).

Additional useful monoclonal antibodies can be generated by standard techniques. Preferably, human

monoclonal antibodies can be produced. Human monoclonal antibodies can be isolated from a combinatorial library produced by the method of Huse et al. (*Science*, 246:1275, 1988). The library can be generated *in vivo* by immunizing nude or SCID mice whose immune system has been reconstituted with human peripheral blood lymphocytes or spleen cells or *in vitro* by immunizing human peripheral blood lymphocytes or spleen cells. The immunogen can be any CD11b or CD18 peptide. Similar techniques are described by Duchosal et al., J. Exp. Med. 92:985 (1990) and Mullinax et al., Proc. Nat'l. Acad. USA 87:8095 (1990).

Peptides derived from the A domain of CD11a, CD11b, or CD11c are preferred immunogens. These peptides can be produced in *E. coli* transformed by a plasmid encoding all or part of the A domain.

A CD18 peptide can also be used as an immunogen. Three anti-CD18 mAbs with anti-inflammatory properties (TS18, 10F12, 60.3) have been identified. Binding each of these antibodies to CD18 can be abrogated by a specific point mutation within a particular region of CD18 (Asp^{128} to Asn^{361} of Fig. 8) (SEQ ID No.: 45). Peptide corresponding to this region can be produced in *E. coli* using a plasmid encoding the A domain.

<u>Assays for CD11b (or CD11c) peptides, heterodimers and monoclonal antibodies</u>

CD11b (or CD11c) peptides, heterodimers, and monoclonal antibodies such as those described above, can be tested *in vitro* for inhibition in one of the following five assays: iC3b binding, inhibition of phagocytosis, inhibition of monocyte/granulocyte adhesion to enclothelium, inhibition of chemotaxis, or inhibition of cell-cell aggregation. Alternatively, they may be tested

in vivo for controlling damage associated with reduced perfusion or immune injury of tissues, as a result of myocardial infarction, burns, frost bite, glomerulonephritis, asthma, adult respiratory distress syndrome, transplant rejection, onset of diabetes mellitus, ischemia, colitis, shock liver syndrome, and resuscitation from hemorrhagic shock.

Inhibition of Granulocyte or Phagocyte Adhesion to iC3b-Coated Erythrocytes or Bacteria

The antimicrobial activity of the neutrophil depends to a significant degree on the ability of this cell to establish a firm attachment to its target. For this purpose, neutrophils possess a number of specific cell surface receptors that promote this interaction, such as a receptor which binds to complement C3 (iC3b), e.g. the CD11b/CD18 receptor. Human neutrophilic polymorphonuclear granulocytes can be isolated from EDTA-anticoagulated blood on Ficoll-Hypaque gradients. Boyum, *Scand. J. Clin. Invest.* (Suppl.) 21:77 (1968) modified as described by Dana et al., *J. Clin. Invest.* 73:153 (1984). Phagocytes can be prepared by incubating the mononuclear cell fraction (obtained from Ficoll-Hypaque centrifugation) on plastic petri dishes. Todd et al., *J. Immunol.* 126:1435 (1981). Peptides of the invention can be tested for their ability to inhibit iC3b mediated binding of granulocytes to sheep erythrocytes as described in Dana et al. *supra*, 1984; and Arnaout et al., *supra*, 1985.

Inhibition of Phagocytosis

Phagocytosis is an important biological function resulting in clearing of damaged tissue from the body, and in elimination of foreign particles (bacteria, fungi). An *in vitro* test for inhibition of phagocytosis

is described in Arnaout et al., *New Eng. J. Med.* 306:693 (1982).

Inhibition Adhesion to Endothelium.

Granulocytes/monocytes must cross vascular endothelium during their egress from blood to extravascular tissues. Studies of leukocyte kinetics in animals indicate that acute inflammatory reactions may be marked by a massive increase in transendothelial monocyte/granulocyte traffic. In many chronic inflammatory lesions, perivascular monocytes accumulate in skin windows more slowly than neutrophils, but later become the predominant cell type. In addition, monocytes leaving the circulation can rapidly acquire the morphology of resident tissue macrophages--in some cases within a few hours of their departure from plasma. Thus, vascular endothelium may be considered an important substrate with which monocytes/granulocytes must interact during adherence, diapedesis, and differentiation. An *in vitro* assay for monocyte/granulocyte interaction with the vessel wall consists of binding radiolabeled or fluorescein monocyte/granulocyte preparations to cultured vascular endothelium, as described in Arnaout et al., *J. Cell Physiol.* 137:305 (1988). Mentzer et al., *J. Cell Physiol.* 125:285 (1986) describes a lymphocyte adhesion assay. These endothelial adhesion assays are appropriate for CD11a, CD11b or CD11c peptides, heterodimers and monoclonal antibodies when the endothelial cells are pre-activated. When the granulocytes/monocytes (or leukocytes) are pre-activated, these assays are suitable for CD11b peptides, heterodimers or monoclonal antibodies.

Inhibition of Chemotaxis.

The ability of cells of the immune system to

migrate is essential to the cellular immune response that results in tissue inflammation. Therefore, a peptide of the invention can be tested for its ability to inhibit chemotaxis, as described in Dana et al., (1986), *supra*.

Cell-Cell Aggregation

A granulocyte aggregation assay can be performed as described by. Arnaout et al., *New Engl. J. Med.* 306:693 (1982). Aggregation can be induced by zymosan-activated autologous serum or with chemotactic peptides, e.g. FMLP. Aggregation can then be recorded as incremental change in light transmission [ΔT] using a platelet aggregometer. The results can be confirmed by phase microscopy.

Assays for CD11a peptides, heterodimers and monoclonal antibodies

CD11a peptides, heterodimers and monoclonal antibodies can be tested using the inhibition of endothelial adhesion assay (described above) or a lymphocyte proliferation assay. Arnaout et al., *J. Clin. Invest.* 74:1291 (1984) describes an assay for inhibition of antigen/mitogen induced lymphocyte proliferation.

In Vivo Model for Testing Peptide

Damage to tissues injured by ischemia-reperfussion (e.g., heart tissue during myocardial infarction) can be minimized by administering to an animal an inhibitor of CD11/CD18 mediated immune response. A peptide of the invention may be tested for *in vivo* effectiveness using animals, e.g., dogs, which have been induced to undergo myocardial infarction. See, e.g. Simpson et al. *supra*.

Use

The peptide or monoclonal antibody can be administered intravenously in saline solution generally

on the order of mg quantities per 10 kilograms of body weight. The peptide can be administered in combination with other drugs, for example, in combination with, or within six hours to three days after a clot dissolving agent, e.g., tissue plasminogen activator (TPA), Activase, or Streptokinase.

SEQUENCE LISTING

(1) GENERAL INFORMATION:

(i) APPLICANT: Arnaout, M. Amin

(ii) TITLE OF INVENTION: Controlling Cellular Immune/Inflamatory Responses with B2 Integrins

(iii) NUMBER OF SEQUENCES: 51

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(A) MEDIUM TYPE: 3.5" Diskette, 1.44 Mb storage
(B) COMPUTER: IBM PS/2 Model 50Z or 55SX
(C) OPERATING SYSTEM: IBM P.C. DOS (Version 3.30)
(D) SOFTWARE: WordPerfect (Version 5.0)

(vi) CURRENT APPLICATION DATA:

(A) APPLICATION NUMBER: 07/637,830
(B) FILING DATE: 01/04/91
(C) CLASSIFICATION:

(vii) PRIOR APPLICATION DATA:

Prior applications total, including application described below: 2

(A) APPLICATION NUMBER: 07/212,573
(B) FILING DATE: 28-06-88

(A) APPLICATION NUMBER: 07/539,842
(B) FILING DATE: 18-06-90

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(2) INFORMATION FOR SEQ ID NO: 1:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	26
(B) TYPE:	amino acid
(D) TOPOLOGY	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 1:

Ala Tyr Phe Gly Ala Ser Leu Cys Ser Val Asp Val Asp Ser Asn
5 10 15

Gly Ser Thr Asp Leu Val Leu Ile Gly Ala Pro
20 25

(2) INFORMATION FOR SEQ ID NO: 2:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	26
(B) TYPE:	amino acid
(D) TOPOLOGY	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 2:

Gly Arg Phe Gly Ala Ala Leu Thr Val Leu Gly Asp Val Asn Gly
5 10 15

Asp Lys Leu Thr Asp Val Ala Ile Gly Ala Pro
20 25

(2) INFORMATION FOR SEQ ID NO: 3:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	26
(B) TYPE:	amino acid
(D) TOPOLOGY:	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 3:

Gln Tyr Phe Gly Gln Ser Leu Ser Gly Gly Gln Asp Leu Thr Met
5 10 15

Asp Gly Leu Val Asp Leu Thr Val Gly Ala Gln
20 25

(2) INFORMATION FOR SEQ ID NO: 4:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 26
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 4:

Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Cys Pro Leu Pro
5 10 15

Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Val
20 25

(2) INFORMATION FOR SEQ ID NO: 5:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 5:

Asp Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His
5 10 15

Asp Phe Arg Arg Met Lys
20

(2) INFORMATION FOR SEQ ID NO: 6:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 6:

Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu Lys
5 10 15

Lys Ser Lys Thr Leu Phe
20

(2) INFORMATION FOR SEQ ID NO: 7:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 7:

Ser Leu Met Gln Tyr Ser Glu Glu Phe Arg Ile His Phe Thr Phe
5 10 15

Lys Glu Phe Gln Asn Asn
20

(2) INFORMATION FOR SEQ ID NO: 8:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 25
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 8:

Pro Asn Pro Arg Ser Leu Val Lys Pro Ile Thr Gln Leu Leu Gly
5 10 15

Arg Thr His Thr Ala Thr Gly Ile Arg Lys
20 25

(2) INFORMATION FOR SEQ ID NO: 9:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 9:

Arg Lys Val Val Arg Glu Leu Phe Asn Ile Thr Asn Gly Ala Arg
5 10 15

Lys Asn Ala Phe Lys
20

(2) INFORMATION FOR SEQ ID NO: 10:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 28
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 10:

Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu Lys Phe Gly Asp
5 10 15

Pro Leu Gly Tyr Glu Asp Val Ile Pro Glu Ala Asp Arg
20 25

(2) INFORMATION FOR SEQ ID NO: 11:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 21
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 11:

Arg Glu Gly Val Ile Arg Tyr Val Ile Gly Val Gly Asp Ala Phe
5 10 15

Arg Ser Glu Lys Ser Arg
20

(2) INFORMATION FOR SEQ ID NO: 12:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid

(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 12:

Gln Glu Leu Asn Thr Ile Ala Ser Lys Pro Pro Arg Asp His Val
5 10 15

Phe Gln Val Asn Asn Phe Glu
20

(2) INFORMATION FOR SEQ ID NO: 13:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 19
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 13:

Ala Leu Lys Thr Ile Gln Asn Gln Leu Arg Glu Lys Ile Phe Ala
5 10 15

Ile Glu Gly Thr

(2) INFORMATION FOR SEQ ID NO: 14:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 14:

Gln Thr Gly Ser Ser Ser Ser Phe Glu His Glu Met Ser Gln Glu
5 10 15

(2) INFORMATION FOR SEQ ID NO: 15:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 8
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 15:

Lys Ser Thr Arg Asp Arg Leu Arg
5

(2) INFORMATION FOR SEQ ID NO: 16:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 16:

Phe Arg Ser Glu Lys Ser Arg Gln Glu Leu Asn Thr Ile Ala Ser
5 10 15

Lys Pro Pro Arg Asp His Val
20

(2) INFORMATION FOR SEQ ID NO: 17:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 17:

Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly Tyr Glu Asp Val Ile
5 10 15

Pro Glu Ala Asp Arg
20

(2) INFORMATION FOR SEQ ID NO: 18:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 18:

Lys Glu Phe Gln Asn Asn Pro Asn Pro Arg Ser Leu
5 10

(2) INFORMATION FOR SEQ ID NO: 19:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 18
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 19:

Gly Thr Gln Thr Gly Ser Ser Ser Ser Phe Glu His Glu Met Ser
5 10 15

Gln Glu Gly

(2) INFORMATION FOR SEQ ID NO: 20:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 23
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 20:

Ser Asn Leu Arg Gln Gln Pro Gln Lys Phe Pro Glu Ala Leu Arg
5 10 15

Gly Cys Pro Gln Glu Asp Ser Asp
20

(2) INFORMATION FOR SEQ ID NO: 21:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 21:

Arg Gln Asn Thr Gly Met Trp Glu Ser Asn Ala Asn Val Lys Gly
5 10 15

Thr

(2) INFORMATION FOR SEQ ID NO: 22:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 22:

Thr Ser Gly Ser Gly Ile Ser Pro Ser His Ser Gln Arg Ile Ala
5 10 15

(2) INFORMATION FOR SEQ ID NO: 23:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 23:

Asn Gln Arg Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr Gly Ser
5 10 15

Cys Glu Pro Ile Arg
20

(2) INFORMATION FOR SEQ ID NO: 24:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 24:

Pro Arg Gly Arg Ala Arg Trp Gln Cys
5

(2) INFORMATION FOR SEQ ID NO: 25:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 20
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 25:

Lys Leu Ser Pro Arg Leu Gln Tyr Phe Gly Gln Ser Leu Ser Gly
5 10 15

Gly Gln Asp Leu Thr
20

(2) INFORMATION FOR SEQ ID NO: 26:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 26:

Gln Lys Ser Thr Arg Asp Arg Leu Arg Glu Gly Gln
5 10

(2) INFORMATION FOR SEQ ID NO: 27:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 22
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 27:

Ser Gly Arg Pro His Ser Arg Ala Val Phe Asn Glu Thr Lys Asn
5 10 15

Ser Thr Arg Arg Gln Thr Gln
20

(2) INFORMATION FOR SEQ ID NO: 28:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 28:

Cys Glu Thr Leu Lys Leu Gln Leu Pro Asn Cys Ile Glu Asp Pro
5 10 15

Val

(2) INFORMATION FOR SEQ ID NO: 29:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 15
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 29:

Phe Glu Lys Asn Cys Gly Asn Asp Asn Ile Cys Gln Asp Asp Leu
5 10 15

(2) INFORMATION FOR SEQ ID NO: 30:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 12
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 30:

Val Arg Asn Asp Gly Glu Asp Ser Tyr Arg Thr Gln
5 10

(2) INFORMATION FOR SEQ ID NO: 31:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 16
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 31

Ser Tyr Arg Lys Val Ser Thr Leu Gln Asn Gln Arg Ser Gln Arg
5 10 15
Ser

(2) INFORMATION FOR SEQ ID NO: 32:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 32:

Asp Ile Ala Phe Leu Ile Asp Gly Ser
5

(2) INFORMATION FOR SEQ ID NO: 33:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 33:

Phe Arg Arg Met Lys Glu Phe Val Ser
5

(2) INFORMATION FOR SEQ ID NO: 34:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 34:

Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu
5 10
(2) INFORMATION FOR SEQ ID NO: 35:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 11
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 35:

Val Ile Arg Tyr Val Ile Gly Val Gly Asp Ala
5 10

(2) INFORMATION FOR SEQ ID NO: 36:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 36:

Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly
5 10

(2) INFORMATION FOR SEQ ID NO: 37:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 10
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 37:

Tyr Glu Asp Val Ile Pro Glu Ala Asp Arg
5 10

(2) INFORMATION FOR SEQ ID NO: 38:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 27
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 38:

Tyr Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Ser Val Cys
5 10 15

Pro Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Tyr
20 25

(2) INFORMATION FOR SEQ ID NO: 39:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5138
(B) TYPE: nucleic acid
(C) STRANDEDNESS: single
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 39:

GAATTCCCTC TTTCACCCTG TCTAGGTTGC CAGCAAATCC CACGGGCCTC 50
CTGACGCTGC CCCTGgGGCC ACAgGTCCCT CGAGTGCTGG AAGG 94
ATG AAG GAT TCC TGC ATC ACT GTG ATG GCC ATG GCG CTG CTG TCT 109
GGG TTC TTT TTC TTC GCG CCG GCC TCG AGC TAC AAC CTG GAC GTG 154
CGG GGC GCG CGG AGC TTC TCC CCA CCG CGC GCC GGG AGG CAC TTT 199
GGA TAC CGC GTC CTG CAG GTC GGA AAC GGG GTC ATC GTG GGA GCT 244
CCA GGG GAG GGG AAC AGC ACA GGA AGC CTC TAT CAG TGC CAG TCG 289
GGC ACA GGA CAC TGC CTG CCA GTC ACC CTG AGA GGT TCC AAC TAT 334
ACC TCC AAG TAC TTG GGC ATG ACC TTG GCA ACA GAC CCC ACA GAT 379
GGA AGC ATT TTG GCC TGT GAC CCT GGG CTG TCT CGA ACG TGT GAC 424
CAG AAC ACC TAT CTG AGT GGC CTG TGT TAC CTC TTC CGC CAG AAT 469
CTG CAG GGT CCC ATG CTG CAG GGG CGC CCT GGT TTT CAG GAA TGT 514
ATC AAG GGC AAC GTA GAC CTG GTA TTT CTG TTT GAT GGT TCG ATG 559
AGC TTG CAG CCA GAT GAA TTT CAG AAA ATT CTG GAC TTC ATG AAG 604
GAT GTG ATG AAG AAA CTC AGC AAC ACT TCG TAC CAG TTT GCT GCT 649
GTT CAG TTT TCC ACA AGC TAC AAA ACA GAA TTT GAT TTC TCA GAT 694
TAT GTT AAA TGG AAG GAC CCT GAT GCT CTG CTG AAG CAT GTA AAG 739
CAC ATG TTG CTG TTG ACA AAT ACC TTT GGT GCC ATC AAT TAT GTC 784
GCG ACA GAG GTG TTC CGG GAG GAG CTG GGG GCC CGG CCA GAT GCC 829
ACC AAA GTG CTT ATC ATC ATC ACG GAT GGG GAG GCC ACT GAC AGT 874
GGC AAC ATC GAT GCG GCC AAA GAC ATC ATC CGC TAC ATC ATC GGG 919
ATT GGA AAG CAT TTT CAG ACC AAG GAG AGT CAG GAG ACC CTC CAC 964
AAA TTT GCA TCA AAA CCC GCG AGC GAG TTT GTG AAA ATT CTG GAC 1009
ACA TTT GAG AAG CTG AAA GAT CTA TTC ATC GAG CGG CAG AAG AAG 1054
ATC TAT GTC ATT GAG GGC ACA AGC AAA CAG GAC CTG ACT TCC TTC 1099
AAC ATG GAG CTG TCC TCC AGC GGC ATC AGT GCT GAC CTC AGC AGG 1144
GGC CAT GCA GTC GTG GGG GCA GTA GGA GCC AAG GAC TGG GCT GGG 1189
GGC TTT CTT GAC CTG AAG GCA GAC CTG CAG GAT GAC ACA TTT ATT 1234
GGG AAT GAA CCA TTG ACA CCA GAA GTG AGA GCA GGC TAT TTG GGT 1279
TAC ACC GTG ACC TGG CTG CCC TCC CGG CAA AAG ACT TCG TTG CTG 1324
GCC TCG GGA GCC CCT CGA TAC CAG CAC ATG GGC CGA GTG CTG CTG 1369
TTC CAA GAG CCA CAG GGC GGA GGA CAC TGG AGC CAG GTC CAG ACA 1414

ATC CAT GGG ACC CAG ATT GGC TCT TAT TTC GGT GGG GAG CTG TGT 1459
GGC GTC GAC GTG GAC CAA GAT GGG GAG ACA GAG CTG CTG CTG ATT 1504
GGT GCC CCA CTG TTC TAT GGG GAG CAG AGA GGA GGC CGG GTG TTT 1549
ATC TAC CAG AGA AGA CAG TTG GGG TTT GAA GAA GTC TCA GAG CTG 1594
CAG GGG GAC CCC GGC TAC CCA CTC GGG CGG TTT GGA GAA GCC ATC 1639
ACT GCT CTG ACA GAC ATC AAC GGC GAT GGG CTG GTA GAC GTG GCT 1684
GTG GGG GCC CCT CTG GAG GAG CAG GGG GCT GTG TAC ATC TTC AAT 1729
GGG AGG CAC GGG GGG CTT AGT CCC CAG CCA AGT CAG CGG ATA GAA 1774
GGG ACC CAA GTG CTC TCA GGA ATT CAG TGG TTT GGA CGC TCC ATC 1819
CAT GGG GTG AAG GAC CTT GAA GGG GAT GGC CTG GCA GAT GTG GCT 1864
GTG GGG GCT GAG AGC CAG ATG ATC GTG CTG AGC TCC CGG CCC GTG 1909
GTG GAT ATG GTC ACC CTG ATG TCC TTC TCT CCA GCT GAG ATC CCA 1954
GTG CAT GAA GTG GAG TCG TCC TAT TCA ACC AGT AAC AAG ATG AAA 1999
GAA GGA GTT AAT ATC ACA ATC TGT TTC CAG ATC AAG TCT CTC TAC 2044
CCC CAG TTC CAA GGC CGC CTG GTT GCC AAT CTC ACT TAC ACT CTG 2089
CAG CTG GAT GGC CAC CGG ACC AGA AGA CGG GGG TTG TTC CCA GGA 2134
GGG AGA CAT GAA CTC AGA AGG AAT ATA GCT GTC ACC ACC AGC ATG 2179
TCA TGC ACT GAC TTC TCA TTT CAT TTC CCG GTA TGT GTT CAA GAC 2224
CTC ATC TCC CCC ATC AAT GTT TCC CTG AAT TTC TCT CTT TGG GAG 2269
GAG GAA GGG ACA CCG AGG GAC CAA AGG GCG CAG GGC AAG GAC ATA 2314
CCG CCC ATC CTG AGA CCC TCC CTG CAC TCG GAA ACC TGG GAG ATC 2359
CCT TTT GAG AAG AAC TGT GGG GAG GAC AAG AAG TGT GAG GCA AAC 2404
TTG AGA GTG TCC TTC TCT CCT GCA ACA TCC AGA GCC CTG CGT CTA 2449
ACT GCT TTT GCC AGC CTC TCT GTG GAG CTG AGC CTG AGT AAC TTG 2494
GAA GAA GAT GCT TAC TGG GTC CAG CTG GAC CTG CAC TTC CCC CCG 2539
GGA CTC TCC TTC CGC AAG GTG GAG ATG CTG AAG CCC CAT AGC CAG 2584
ATA CCT GTG AGC TGC GAG GAG CTT CCT GAA GAG TCC AGG CTT CTG 2629
TCC AGG GCA TTA TCT TGC AAT GTG AGC TCT CCC ATC TTC AAA GCA 2674
GGC CAC TCG GTT GCT CTG CAG ATG ATG TTT AAT ACA CTG GTA AAC 2719
AGC TCC TGG GGG GAC TCG GTT GAA TTG CAC GCC AAT GTG ACC TGT 2764
AAC AAT GAG GAC TCA GAC CTC CTG GAG GAC AAC TCA GCC ACT ACC 2809
ATC ATC CCC ATC CTG TAC CCC ATC AAC ATC CTC ATC CAG GAC CAA 2854
GAA GAC TCC ACA CTC TAT GTC AGT TTC ACC CCC AAA GGC CCC AAG 2899
ATC CAC CAA GTC AAG CAC ATG TAC CAG GTG AGG ATC CAG CCT TCC 2944
ATC CAC GAC CAC AAC ATA CCC ACC CTG GAG GCT GTG GTT GGG GTG 2989
CCA CAG CCT CCC AGC GAG GGG CCC ATC ACA CAC CAG TGG AGC GTG 3034
CAG ATG GAG CCT CCC GTG CCC TGC CAC TAT GAG GAT CTG GAG AGG 3079
CTC CCG GAT GCA GCT GAG CCT TGT CTC CCC GGA CCC CTG TTC CGC 3124
TGC CCT GTT GTC TTC AGG CAG GAG ATC CTC GTC CAA GTG ATC GGG 3169
ACT CTG GAG CTG GTG GGA GAG ATC GAG GCC TCT TCC ATG TTC AGC 3214
CTC TGC AGC TCC CTC TCC ATC TCC TTC AAC AGC AGC AAG CAT TTC 3259
CAC CTC TAT GGC AGC AAC GCC TCC CTG GCC CAG GTT GTC ATG AAG 3304
GTT GAC GTG GTG TAT GAG AAG CAG ATG CTC TAC CTC TAC GTG CTG 3349
AGC GGC ATC GGG GGG CTG CTG CTG CTG CTG CTC ATT TIC ATA GTG 3394
CTG TAC AAG GTT GGT TTC TTC AAA CGG AAC CTG AAG GAG AAG ATG 3439
GAG GCT GGC AGA GGT GTC CCG AAT GGA ATC CCT GCA GAA GAC TCT 3484
GAG CAG CTG GCA TCT GGG CAA GAG GCT GGG GAT CCC GGC TGC CTG 3529
AAG CCC CTC CAT GAG AAG GAC TCT GAG AGT GGT GGT GGC AAG GAC 3574
TGAGTCCAGC CTGTGAGGTG CAGAGTGCCC AGAACTGGAC TCAGGATGCC 3624
CAGGGCCACT TCGCCTCTGC CTGCATTCTG CCGTGTGCCC TCGGGCGAGT 3674
CACTGCCTCT CCCTGGCCCT CAGTTTCCCT ATCTCGAACA TGGAACTCAT 3724
TCCTGAATGT CTCCTTTGCA GGCTCATAGG GAAGACCTGC TGAGGGACCA 3774
GCCAAGAGGG CTGCAAAAGT GAGGGCTTGT CATTACCAGA CGGTTCACCA 3824

GCCTCTCTTG GTTCCTTCCT TGGAAGAGAA TGTCTGATCT AAATGTGGAG 3874
AAACTGTAGT CTCAGGACCT AGGGATGTTC TGGCCCTCAC CCCTGCCCTG 3924
GGATGTCCAC AGATGCCTCC ACCCCCCAGA ACCTGTCCTT GCACACTCCC 3974
CTGCACTGGA GTCCAGTCTC TTCTGTTGGC AGAAAGCAAA TGTGACCTGT 4024
GTCACTACGT GACTGTGGCA CACGCCTTGT TCTTGGCCAA AGACCAAATT 4074
CCTTGGCATG CCTTCCAGCA CCCTGCAAAA TGAGACCCTC GTGGCCTTCC 4124
CCAGCCTCTT CTAGAGCCGT GATGCCTCCC TGTTGAAGCT CTGGTGACAC 4174
CAGCCTTTCT CCCAGGCCAG GCTCCTTCCT GTCTTCCTGC ATTCACCCAG 4224
ACAGCTCCCT CTGCCTGAAC CTTCCATCTC GCCCACCCCT CCTTCCTTGA 4274
CCAGCAGATC CCAGCTCACG TCACACACTT GGTTGGGTCC TCACATCTTT 4324
CACACTTCCA CCACCCTGCA CTACTCCCTC AAAGCACACG TCATGTTTCT 4374
TCATCCGGCA GCCTGGATGT TTTTTCCCTG TTTAATGATT GACGTACTTA 4424
GCAGCTATCT CTCAGTGAAC TGTGAGGGTA AAGGCTATAC TTGTCTTGTT 4474
CACCTTGGGA TGACGCCGCA TGATATGTCA GGGCGTGGGA CATCTAGTAG 4524
GTGCTTGACA TAATTTCACT GAATTAATGA CAGAGCCAGT GGGAAGATAC 4574
AGAAAAAGAG GGCCGGGGCT GGGCGCGGTG GTTCACGCCT GTAATCCCAG 4624
CACTTTGGGA GGCCAAGGAG GGTGGATCAC CTGAGGTCAG GAGTTAGAGG 4674
CCAGCCTGGC GAAACCCCAT CTCTACTAAA AATACAAAAT CCAGGCGTGG 4724
TGGCACACAC CTGTAGTCCC AGCTACTCAG GAGGTTGAGG TAGGAGAATT 4774
GCTTGAACCT GGGAGGTGGA GGTTGCAGTG AGCCAAGATT GCGCCATTGC 4824
ACTCCAGCCT GGGCAACACA GCGAGACTCC GTCTCAAGGA AAAAATAAAA 4874
ATAAAAAGCG GGCACGGGCC CGGACATCCC CACCCTTGGA GGCTGTCTTC 4924
TCAGGCTCTG CCCTGCCCTA GCTCCACACC CTCTCCCAGG ACCCATCACG 4974
CCTGTGCAGT GGCCCCCACA GAAAGACTGA GCTCAAGGTG GGAACCACGT 5024
CTGCTAACTT GGAGCCCCAG TGCCAAGCAC AGTGCCTGCA TGTATTTATC 5074
CAATAAATGT GAAATTCTGT CCAAAAAAAA AAAA 5108

(2) INFORMATION FOR SEQ ID NO: 40:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	3533
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 40:

tggcttcctt gtggttcctc agtggtgcct gcaacccctg gttcacctcc 50
ttccaggttc tggcccttcc agcc 74
atg gct ctc aga gtc ctt ctg tta aca gcc ttg acc tta tgt cat 89
ggg ttc aac ttg gac act gaa aac gca atg acc ttc caa gag aac 134
gca agg ggc ttc ggg cag agc gtg gtc cag ctt cag gga tcc agg 179
gtg gtg gtt gga gcc ccc cag gag ata gtg gct gcc aac caa agg 224
ggc agc ctc tac cag tgc gac tac agc aca ggc tca tgc gag ccc 269
atc cgc ctg cag gtc ccc gtg gag gcc gtg aac atg tcc ctg ggc 314
ctg tcc ctg gca gcc acc acc agc ccc cct cag ctg ctg gcc tgt 359
ggt ccc acc gtg cac cag act tgc agt gag aac acg tat gtg aaa 404
ggg ctc tgc ttc ctg ttt gga tcc aac cta cgg cag cag ccc cag 449
aag ttc cca gag gcc ctc cga ggg tgt cct caa gag gat agt gac 494
att gcc ttc ttg att gat ggc tct ggt agc atc atc cca cat gac 539
ttt cgg cgg atg aag gag ttt gtc tca act gtg atg gag caa tta 584
aaa aag tcc aaa acc ttg ttc tct ttg atg cag tac tct gaa gaa 629

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ttc cgg att cac ttt acc ttc aaa gag ttc cag aac aac cct aac   674
cca aga tca ctg gtg aag cca ata acg cag ctg ctt ggg cgg aca   719
cac acg gcc acg ggc atc cgc aaa gtg gta cga gag ctg ttt aac   764
atc acc aac gga gcc cga aag aat gcc ttt aag atc cta gtt gtc   809
atc acg gat gga gaa aag ttt ggc gat ccc ttg gga tat gag gat   854
gtc atc cct gag gca gac aga gag gga gtc att cgc tac gtc att   899
ggg gtg gga gat gcc ttc cgc agt gag aaa tcc cgc caa gag ctt   944
aat acc atc gca tcc aag ccg cct cgt gat cac gtg ttc cag gtg   989
aat aac ttt gag gct ctg aag acc att cag aac cag ctt cgg gag  1034
aag atc ttt gcg atc gag ggt act cag aca gga agt agc agc tcc  1079
ttt gag cat gag atg tct cag gaa ggc ttc agc gct gcc atc acc  1124
tct aat ggc ccc ttg ctg agc act gtg ggg agc tat gac tgg gct  1169
ggt gga gtc ttt cta tat aca tca aag gag aaa agc acc ttc atc  1214
aac atg acc aga gtg gat tca gac atg aat gat gct tac ttg ggt  1259
tat gct gcc gcc atc atc tta cgg aac cgg gtg caa agc ctg gtt  1304
ctg ggg gca cct cga tat cag cac atc ggc ctg gta gcg atg ttc  1349
agg cag aac act ggc atg tgg gag tcc aac gct aat gtc aag ggc  1394
acc cag atc ggc gcc tac ttc ggg gcc tcc ctc tgc tcc gtg gac  1439
gtg gac agc aac ggc agc acc gac ctg gtc ctc atc ggg gcc ccc  1484
cat tac tac gag cag acc cga ggg ggc cag gtg tcc gtg tgc ccc  1529
ttg ccc agg ggg agg gct cgg tgg cag tgt gat gct gtt ctc tac  1574
ggg gag cag ggc caa ccc tgg ggc cgc ttt ggg gca gcc cta aca  1619
gtg ctg ggg gac gta aat ggg gac aag ctg acg gac gtg gcc att  1664
ggg gcc cca gga gag gag gac aac cgg ggt gct gtt tac ctg ttt  1709
cac gga acc tca gga tct ggc atc agc ccc tcc cat agc cag cgg  1754
ata gca ggc tcc aag ctc tct ccc agg ctc cag tat ttt ggt cag  1799
tca ctg agt ggg ggc cag gac ctc aca atg gat gga ctg gta gac  1844
ctg act gta gga gcc cag ggg cac gtg ctg ctg ctc agg tcc cag  1889
cca gta ctg aga gtc aag gca atc atg gag ttc aat ccc agg gaa  1934
gtg gca agg aat gta ttt gag tgt aat gat caa gtg gtg aaa ggc  1979
aag gaa gcc gga gag gtc aga gtc tgc ctc cat gtc cag aag agc  2024
aca cgg gat cgg cta aga gaa gga cag atc cag agt gtt gtg act  2069
tat gac ctg gct ctg gac tcc ggc cgc cca cat tcc cgc gcc gtc  2114
ttc aat gag aca aag aac agc aca cgc aga cag aca cag gtc ttg  2159
ggg ctg acc cag act tgt gag acc ctg aaa cta cag ttg ccg aat  2204
tgc atc gag gac cca gtg agc ccc att gtg ctg cgc ctg aac ttc  2249
tct ctg gtg gga acg cca ttg tct gct ttc ggg aac ctc cgg cca  2294
gtg ctg gcg gag gat gct cag aga ctc ttc aca gcc ttg ttt ccc  2339
ttt gag aag aat tgt ggc aat gac aac atc tgc cag gat gac ctc  2384
agc atc acc ttc agt ttc atg agc ctg gac tgc ctc gtg gtg ggt  2429
ggg ccc cgg gag tct aac gtg aca gtg act gtg aga aat gat ggt  2474
gag gac tcc tac agg aca cag gtc acc ttc ttc ttc ccg ctt gac  2519
ctg tcc tac cgg aag gtg tcc aca ctc cag aac cag cgc tca cag  2564
cga tcc tgg cgc ctg gcc tgt gag tct gcc tcc tcc acc gaa gtg  2609
tct ggg gcc ttg aag agc acc agc tgc agc ata aac cac ccc atc  2654
ttc ccg gaa aac tca gag gtc acc ttt aat atc acg ttt gat gta  2699
gac tct aag gct tcc ctt gga aac aaa ctg ctc ctc aag gcc aat  2744
gtg acc agt gag aac aac atg ccc aga acc aac aaa acc gaa ttc  2789
caa ctg gag ctg ccg gtg aaa tat gct gtc tac atg gtg gtc acc  2834
agc cat ggg gtc tcc act aaa tat ctc aac ttc acg gcc tca gag  2879
aat acc agt cgg gtc atg cag cat caa tat cag gtc agc aac ctg  2924
ggg cag agg agc ccc ccc atc agc ctg gtg ttc ttg gtg ccc gtc  2969
cgg ctg aac cag act gtc ata tgg gac cgc ccc cag gtc acc ttc  3014
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tcc gag aac ctc tcg agt acg tgc cac acc aag gag cgc ttg ccc 3059
tct cac tcc gac ttt ctg gct gag ctt cgg aag gcc ccc gtg gtg 3104
aac tgc tcc atc gct gtc tgc cag aga atc cag tgt gac atc ccg 3149
ttc ttt ggc atc cag gaa gaa ttc aat gct acc ctc aaa ggc aac 3194
ctc tcg ttt gac tgg tac atc aag acc tcg cat aac cac ctc ctg 3239
atc gtg agc aca gct gag atc ttg ttt aac gat tcc gtg ttc acc 3284
ctg ctg ccg gga cag ggg gcg ttt gtg agg tcc cag acg gag acc 3329
aaa gtg gag ccg ttc gag gtc ccc aac ccc ctg ccg ctc atc gtg 3374
ggc agc tct gtc ggg gga ctg ctg ctc ctg gcc ctc atc acc gcc 3419
gcg ctg tac aag ctc ggc ttc ttc aag cgg caa tac aag gac atg 3464
atg agt gaa ggg ggt ccc ccg ggg gcc gaa ccc cag tag 3503

(2) INFORMATION FOR SEQ ID NO: 41:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	2310
(B) TYPE:	nucleic acid
(C) STRANDEDNESS:	single
(D) TOPOLOGY:	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 41:

ATG CTG GGC CTG CGC CCC CCA CTT CTC GCC CTG GTG GGG CTG CTC 45
TCC CTC GGG TGC GTC CTC TCT CAG GAG TGC ACG AAG TTC AAG GTC 90
AGC AGC TGC CGG GAA TGC ATC GAG TCG GGG CCC GGC TGC ACC TGG 135
TGC CAG AAG CTG AAC TTC ACA GGG CCG GGG GAT CCT GAC TCC ATT 180
CGC TGC GAC ACC CGG CCA CAG CTG CTC ATG AGG GGC TGT GCG GCT 225
GAC GAC ATC ATG GAC CCC ACA AGC CTC GCT GAA ACC CAG GAA GAC 270
CAC AAT GGG GGC CAG AAG CAG CTG TCC CCA CAA AAA GTG ACG CTT 315
TAC CTG CGA CCA GGC CAG GCA GCA GCG TTC AAC GTG ACC TTC CGG 360
CGG GCC AAG GGC TAC CCC ATC GAC CTG TAC TAT CTG ATG GAC CTC 405
TCC TAC TCC ATG CTT GAT GAC CTC AGG AAT GTC AAG AAG CTA GGT 450
GGC GAC CTG CTC CGG GCC CTC AAC GAG ATC ACC GAG TCC GGC CGC 495
ATT GGC TTC GGG TCC TTC GTG GAC AAG ACC GTG CTG CCG TTC GTG 540
AAC ACG CAC CCT GAT AAG CTG CGA AAC CCA TGC CCC AAC AAG GAG 585
AAA GAG TGC CAG CCC CCG TTT GCC TTC AGG CAC GTG CTG AAG CTG 630
ACC AAC AAC TCC AAC CAG TTT CAG ACC GAG GTC GGG AAG CAG CTG 675
ATT TCC GGA AAC CTG GAT GCA CCC GAG GGT GGG CTG GAC GCC ATG 720
ATG CAG GTC GCC GCC TGC CCG GAG GAA ATC GGC TGG CGC AAC GTC 765
ACG CGG CTG CTG GTG TTT GCC ACT GAT GAC GGC TTC CAT TTC GCG 810
GGC GAC GGA AAG CTG GGC GCC ATC CTG ACC CCC AAC GAC GGC CGC 855
TGT CAC CTG GAG GAC AAC TTG TAC AAG AGG AGC AAC GAA TTC GAC 900
TAC CCA TCG GTG GGC CAG CTG GCG CAC AAG CTG GCT GAA AAC AAC 945
ATC CAG CCC ATC TTC GCG GTG ACC AGT AGG ATG GTG AAG ACC TAC 990
GAG AAA CTC ACC GAG ATC ATC CCC AAG TCA GCC GTG GGG GAG CTG 1035
TCT GAG GAC TCC AGC AAT GTG GTC CAT CTC ATT AAG AAT GCT TAC 1080
AAT AAA CTC TCC TCC AGG GTC TTC CTG GAT CAC AAC GCC CTC CCC 1125
GAC ACC CTG AAA GTC ACC TAC GAC TCC TTC TGC AGC AAT GGA GTG 1170
ACG CAC AGG AAC CAG CCC AGA GGT GAC TGT GAT GGC GTG CAG ATC 1215
AAT GTC CCG ATC ACC TTC CAG GTG AAG GTC ACG GCC ACA GAG TGC 1260

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ATC CAG GAG CAG TCG TTT GTC ATC CGG GCG CTG GGC TTC ACG GAC  1305
ATA GTG ACC GTG CAG GTT CTT CCC CAG TGT GAG TGC CGG TGC CGG  1350
GAC CAG AGC AGA GAC CGC AGC CTC TGC CAT GGC AAG GGC TTC TTG  1395
GAG TGC GGC ATC TGC AGG TGT GAC ACT GGC TAC ATT GGG AAA AAC  1440
TGT GAG TGC CAG ACA CAG GGC CGG AGC AGC CAG GAG CTG GAA GGA  1485
AGC TGC CGG AAG GAC AAC AAC TCC ATC ATC TGC TCA GGG CTG GGG  1530
GAC TGT GTC TGC GGG CAG TGC CTG TGC CAC ACC AGC GAC GTC CCC  1575
GGC AAG CTG ATA TAC GGG CAG TAC TGC GAG TGT GAC ACC ATC AAC  1620
TGT GAG CGC TAC AAC GGC CAG GTC TGC GGC GGC CCG GGG AGG GGG  1665
CTC TGC TTC TGC GGG AAG TGC CGC TGC CAC CCG GGC TTT GAG GGC  1710
TCA GCG TGC CAG TGC GAG AGG ACC ACT GAG GGC TGC CTG AAC CCG  1755
CGG CGT GTT GAG TGT AGT GGT CGT GGC CGG TGC CGC TGC AAC GTA  1800
TGC GAG TGC CAT TCA GGC TAC CAG CTG CCT CTG TGC CAG GAG TGC  1845
CCC GGC TGC CCC TCA CCC TGT GGC AAG TAC ATC TCC TGC GCC GAG  1890
TGC CTG AAG TTC GAA AAG GGC CCC TTT GGG AAG AAC TGC AGC GCG  1935
GCG TGT CCG GGC CTG CAG CTG TCG AAC AAC CCC GTG AAG GGC AGG  1980
ACC TGC AAG GAG AGG GAC TCA GAG GGC TGC TGG GTG GCC TAC ACG  2025
CTG GAG CAG CAG GAC GGG ATG GAC CGC TAC CTC ATC TAT GTG GAT  2070
GAG AGC CGA GAG TGT GTG GCA GGC CCC AAC ATC GCC GCC ATC GTC  2115
GGG GGC ACC GTG GCA GGC ATC GTG CTG ATC GGC ATT CTC CTG CTG  2160
GTC ATC TGG AAG GCT CTG ATC CAC CTG AGC GAC CTC CGG GAG TAC  2205
AGG CGC TTT GAG AAG GAG AAG CTC AAG TCC CAG TGG AAC AAT GAT  2250
AAT CCC CTT TTC AAG AGC GCC ACC ACG ACG GTC ATG AAC CCC AAG  2295
TTT GCT GAG AGT TAG                                        2300
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(2) INFORMATION FOR SEQ ID NO: 42:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH:	1170
(B) TYPE:	amino acid
(D) TOPOLOGY:	linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 42:

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Met Lys Asp Ser Cys Ile Thr Val Met Ala Met Ala Leu Leu Ser
 5                  10                  15

Gly Phe Phe Phe Phe Ala Pro Ala Ser Ser Tyr Asn Leu Asp Val
            20                  25                  30

Arg Gly Ala Arg Ser Phe Ser Pro Pro Arg Ala Gly Arg His Phe
        35                  40                  50

Gly Tyr Arg Val Leu Gln Val Gly Asn Gly Val Ile Val Gly Ala
    55                  60                  65

Pro Gly Glu Gly Asn Ser Thr Gly Ser Leu Tyr Gln Cys Gln Ser
70                  75                  80

Gly Thr Gly His Cys Leu Pro Val Thr Leu Arg Gly Ser Asn Tyr
            85                  90                  95
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Thr Ser Lys Tyr Leu Gly Met Thr Leu Ala Thr Asp Pro Thr Asp
100 105 115

Gly Ser Ile Leu Ala Cys Asp Pro Gly Leu Ser Arg Thr Cys Asp
120 125 130

Gln Asn Thr Tyr Leu Ser Gly Leu Cys Tyr Leu Phe Arg Gln Asn
135 140 145

Leu Gln Gly Pro Met Leu Gln Gly Arg Pro Gly Phe Gln Glu Cys
150 155 160

Ile Lys Gly Asn Val Asp Leu Val Phe Leu Phe Asp Gly Ser Met
165 170 175

Ser Leu Gln Pro Asp Glu Phe Gln Lys Ile Leu Asp Phe Met Lys
180 185 190

Asp Val Met Lys Lys Leu Ser Asn Thr Ser Tyr Gln Phe Ala Ala
195 200 205

Val Gln Phe Ser Thr Ser Tyr Lys Thr Glu Phe Asp Phe Ser Asp
215 220 225

Tyr Val Lys Trp Lys Asp Pro Asp Ala Leu Leu Lys His Val Lys
230 235 240

His Met Leu Leu Leu Thr Asn Thr Phe Gly Ala Ile Asn Tyr Val
245 250 255

Ala Thr Glu Val Phe Arg Glu Glu Leu Gly Ala Arg Pro Asp Ala
260 265 270

Thr Lys Val Leu Ile Ile Ile Thr Asp Gly Glu Ala Thr Asp Ser
275 280 285

Gly Asn Ile Asp Ala Ala Lys Asp Ile Ile Arg Tyr Ile Ile Gly
290 295 300

Ile Gly Lys His Phe Gln Thr Lys Glu Ser Gln Glu Thr Leu His
305 310 315

Lys Phe Ala Ser Lys Pro Ala Ser Glu Phe Val Lys Ile Leu Asp
320 325 330

Thr Phe Glu Lys Leu Lys Asp Leu Phe Ile Glu Arg Gln Lys Lys
335 340 345

Ile Tyr Val Ile Glu Gly Thr Ser Lys Gln Asp Leu Thr Ser Phe
350 355 360

Asn Met Glu Leu Ser Ser Ser Gly Ile Ser Ala Asp Leu Ser Arg

365 370 375

Gly His Ala Val Val Gly Ala Val Gly Ala Lys Asp Trp Ala Gly
380 385 390

Gly Phe Leu Asp Leu Lys Ala Asp Leu Gln Asp Asp Thr Phe Ile
395 400 405

Gly Asn Glu Pro Leu Thr Pro Glu Val Arg Ala Gly Tyr Leu Gly
415 420 425

Tyr Thr Val Thr Trp Leu Pro Ser Arg Gln Lys Thr Ser Leu Leu
430 435 440

Ala Ser Gly Ala Pro Arg Tyr Gln His Met Gly Arg Val Leu Leu
445 450 455

Phe Gln Glu Pro Gln Gly Gly Gly His Trp Ser Gln Val Gln Thr
460 465 470

Ile His Gly Thr Gln Ile Gly Ser Tyr Phe Gly Gly Glu Leu Cys
475 480 485

Gly Val Asp Val Asp Gln Asp Gly Glu Thr Glu Leu Leu Leu Ile
490 495 500

Gly Ala Pro Leu Phe Tyr Gly Glu Gln Arg Gly Gly Arg Val Phe
505 510 515

Ile Tyr Gln Arg Arg Gln Leu Gly Phe Glu Glu Val Ser Glu Leu
520 525 530

Gln Gly Asp Pro Gly Tyr Pro Leu Gly Arg Phe Gly Glu Ala Ile
535 540 545

Thr Ala Leu Thr Asp Ile Asn Gly Asp Gly Leu Val Asp Val Ala
550 555 560

Val Gly Ala Pro Leu Glu Glu Gln Gly Ala Val Tyr Ile Phe Asn
565 570 575

Gly Arg His Gly Gly Leu Ser Pro Gln Pro Ser Gln Arg Ile Glu
580 585 590

Gly Thr Gln Val Leu Ser Gly Ile Gln Trp Phe Gly Arg Ser Ile
595 600 605

His Gly Val Lys Asp Leu Glu Gly Asp Gly Leu Ala Asp Val Ala
610 615 620

Val Gly Ala Glu Ser Gln Met Ile Val Leu Ser Ser Arg Pro Val
625 630 635

Val Asp Met Val Thr Leu Met Ser Phe Ser Pro Ala Glu Ile Pro
640 645 650

Val His Glu Val Glu Ser Ser Tyr Ser Thr Ser Asn Lys Met Lys
655 670 675

Glu Gly Val Asn Ile Thr Ile Cys Phe Gln Ile Lys Ser Leu Tyr
680 685 690

Pro Gln Phe Gln Gly Arg Leu Val Ala Asn Leu Thr Tyr Thr Leu
695 670 675

Gln Leu Asp Gly His Arg Thr Arg Arg Arg Gly Leu Phe Pro Gly
680 685 690

Gly Arg His Glu Leu Arg Arg Asn Ile Ala Val Thr Thr Ser Met
695 700 705

Ser Cys Thr Asp Phe Ser Phe His Phe Pro Val Cys Val Gln Asp
710 715 720

Leu Ile Ser Pro Ile Asn Val Ser Leu Asn Phe Ser Leu Trp Glu
725 730 735

Glu Glu Gly Thr Pro Arg Asp Gln Arg Ala Gln Gly Lys Asp Ile
740 745 750

Pro Pro Ile Leu Arg Pro Ser Leu His Ser Glu Thr Trp Glu Ile
755 760 765

Pro Phe Glu Lys Asn Cys Gly Glu Asp Lys Lys Cys Glu Ala Asn
770 775 780

Leu Arg Val Ser Phe Ser Pro Ala Thr Ser Arg Ala Leu Arg Leu
785 790 795

Thr Ala Phe Ala Ser Leu Ser Val Glu Leu Ser Leu Ser Asn Leu
800 805 810

Glu Glu Asp Ala Tyr Trp Val Gln Leu Asp Leu His Phe Pro Pro
815 820 825

Gly Leu Ser Phe Arg Lys Val Glu Met Leu Lys Pro His Ser Gln
830 835 840

Ile Pro Val Ser Cys Glu Glu Leu Pro Glu Glu Ser Arg Leu Leu
845 850 855

Ser Arg Ala Leu Ser Cys Asn Val Ser Ser Pro Ile Phe Lys Ala
860 865 870

Gly His Ser Val Ala Leu Gln Met Met Phe Asn Thr Leu Val Asn
875 880 885

Ser Ser Trp Gly Asp Ser Val Glu Leu His Ala Asn Val Thr Cys
890 895 900

Asn Asn Glu Asp Ser Asp Leu Leu Glu Asp Asn Ser Ala Thr Thr
905 910 915

Ile Ile Pro Ile Leu Tyr Pro Ile Asn Ile Leu Ile Gln Asp Gln
920 925 930

Glu Asp Ser Thr Leu Tyr Val Ser Phe Thr Pro Lys Gly Pro Lys
935 940 945

Ile His Gln Val Lys His Met Tyr Gln Val Arg Ile Gln Pro Ser
950 955 960

Ile His Asp His Asn Ile Pro Thr Leu Glu Ala Val Val Gly Val
965 970 975

Pro Gln Pro Pro Ser Glu Gly Pro Ile Thr His Gln Trp Ser Val
980 985 990

Gln Met Glu Pro Pro Val Pro Cys His Tyr Glu Asp Leu Glu Arg
995 1000 1005

Leu Pro Asp Ala Ala Glu Pro Cys Leu Pro Gly Pro Leu Phe Arg
1010 1015 1020

Cys Pro Val Val Phe Arg Gln Glu Ile Leu Val Gln Val Ile Gly
1025 1030 1035

Thr Leu Glu Leu Val Gly Glu Ile Glu Ala Ser Ser Met Phe Ser
1040 1045 1050

Leu Cys Ser Ser Leu Ser Ile Ser Phe Asn Ser Ser Lys His Phe
1055 1060 1065

His Leu Tyr Gly Ser Asn Ala Ser Leu Ala Gln Val Val Met Lys
1070 1075 1080

Val Asp Val Val Tyr Glu Lys Gln Met Leu Tyr Leu Tyr Val Leu
1085 1090 1095

Ser Gly Ile Gly Gly Leu Leu Leu Leu Leu Leu Ile Xaa Ile Val
1100 1105 1110

Leu Tyr Lys Val Gly Phe Phe Lys Arg Asn Leu Lys Glu Lys Met
1115 1120 1125

Glu Ala Gly Arg Gly Val Pro Asn Gly Ile Pro Ala Glu Asp Ser
1130 1135 1140

Glu Gln Leu Ala Ser Gly Gln Glu Ala Gly Asp Pro Gly Cys Leu

1145 1150 1155

Lys Pro Leu His Glu Lys Asp Ser Glu Ser Gly Gly Gly Lys Asp
1160 1165 1170

(2) INFORMATION FOR SEQ ID NO: 43:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1152
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 43:

Met Ala Leu Arg Val Leu Leu Leu Thr Ala Leu Thr Leu Cys His
5 10 15

Gly Phe Asn Leu Asp Thr Glu Asn Ala Met Thr Phe Gln Glu Asn
20 25 30

Ala Arg Gly Phe Gly Gln Ser Val Val Gln Leu Gln Gly Ser Arg
35 40 50

Val Val Val Gly Ala Pro Gln Glu Ile Val Ala Ala Asn Gln Arg
55 60 65

Gly Ser Leu Tyr Gln Cys Asp Tyr Ser Thr Gly Ser Cys Glu Pro
70 75 80

Ile Arg Leu Gln Val Pro Val Glu Ala Val Asn Met Ser Leu Gly
85 90 95

Leu Ser Leu Ala Ala Thr Thr Ser Pro Pro Gln Leu Leu Ala Cys
100 105 115

Gly Pro Thr Val His Gln Thr Cys Ser Glu Asn Thr Tyr Val Lys
120 125 130

Gly Leu Cys Phe Leu Phe Gly Ser Asn Leu Arg Gln Gln Pro Gln
135 140 145

Lys Phe Pro Glu Ala Leu Arg Gly Cys Pro Gln Glu Asp Ser Asp
150 155 160

Ile Ala Phe Leu Ile Asp Gly Ser Gly Ser Ile Ile Pro His Asp
165 170 175

Phe Arg Arg Met Lys Glu Phe Val Ser Thr Val Met Glu Gln Leu
180 185 190

Lys Lys Ser Lys Thr Leu Phe Ser Leu Met Gln Tyr Ser Glu Glu
195 200 205

Phe Arg Ile His Phe Thr Phe Lys Glu Phe Gln Asn Asn Pro Asn
215 220 225

Pro Arg Ser Leu Val Lys Pro Ile Thr Gln Leu Leu Gly Arg Thr
230 235 240

His Thr Ala Thr Gly Ile Arg Lys Val Val Arg Glu Leu Phe Asn
245 250 255

Ile Thr Asn Gly Ala Arg Lys Asn Ala Phe Lys Ile Leu Val Val
260 265 270

Ile Thr Asp Gly Glu Lys Phe Gly Asp Pro Leu Gly Tyr Glu Asp
275 280 285

Val Ile Pro Glu Ala Asp Arg Glu Gly Val Ile Arg Tyr Val Ile
290 295 300

Gly Val Gly Asp Ala Phe Arg Ser Glu Lys Ser Arg Gln Glu Leu
305 310 315

Asn Thr Ile Ala Ser Lys Pro Pro Arg Asp His Val Phe Gln Val
320 325 330

Asn Asn Phe Glu Ala Leu Lys Thr Ile Gln Asn Gln Leu Arg Glu
335 340 345

Lys Ile Phe Ala Ile Glu Gly Thr Gln Thr Gly Ser Ser Ser Ser
350 355 360

Phe Glu His Glu Met Ser Gln Glu Gly Phe Ser Ala Ala Ile Thr
365 370 375

Ser Asn Gly Pro Leu Leu Ser Thr Val Gly Ser Tyr Asp Trp Ala
380 385 390

Gly Gly Val Phe Leu Tyr Thr Ser Lys Glu Lys Ser Thr Phe Ile
395 400 405

Asn Met Thr Arg Val Asp Ser Asp Met Asn Asp Ala Tyr Leu Gly
415 420 425

Tyr Ala Ala Ala Ile Ile Leu Arg Asn Arg Val Gln Ser Leu Val
430 435 440

Leu Gly Ala Pro Arg Tyr Gln His Ile Gly Leu Val Ala Met Phe
445 450 455

Arg Gln Asn Thr Gly Met Trp Glu Ser Asn Ala Asn Val Lys Gly

460 465 470

Thr Gln Ile Gly Ala Tyr Phe Gly Ala Ser Leu Cys Ser Val Asp
475 480 485

Val Asp Ser Asn Gly Ser Thr Asp Leu Val Leu Ile Gly Ala Pro
490 495 500

His Tyr Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Cys Pro
505 510 515

Leu Pro Arg Gly Arg Ala Arg Trp Gln Cys Asp Ala Val Leu Tyr
520 525 530

Gly Glu Gln Gly Gln Pro Trp Gly Arg Phe Gly Ala Ala Leu Thr
535 540 545

Val Leu Gly Asp Val Asn Gly Asp Lys Leu Thr Asp Val Ala Ile
550 555 560

Gly Ala Pro Gly Glu Glu Asp Asn Arg Gly Ala Val Tyr Leu Phe
565 570 575

His Gly Thr Ser Gly Ser Gly Ile Ser Pro Ser His Ser Gln Arg
580 585 590

Ile Ala Gly Ser Lys Leu Ser Pro Arg Leu Gln Tyr Phe Gly Gln
595 600 605

Ser Leu Ser Gly Gly Gln Asp Leu Thr Met Asp Gly Leu Val Asp
610 615 620

Leu Thr Val Gly Ala Gln Gly His Val Leu Leu Leu Arg Ser Gln
625 630 635

Pro Val Leu Arg Val Lys Ala Ile Met Glu Phe Asn Pro Arg Glu
640 645 650

Val Ala Arg Asn Val Phe Glu Cys Asn Asp Gln Val Val Lys Gly
655 670 675

Lys Glu Ala Gly Glu Val Arg Val Cys Leu His Val Gln Lys Ser
680 685 690

Thr Arg Asp Arg Leu Arg Glu Gly Gln Ile Gln Ser Val Val Thr
695 670 675

Tyr Asp Leu Ala Leu Asp Ser Gly Arg Pro His Ser Arg Ala Val
680 685 690

Phe Asn Glu Thr Lys Asn Ser Thr Arg Arg Gln Thr Gln Val Leu
695 700 705

Gly Leu Thr Gln Thr Cys Glu Thr Leu Lys Leu Gln Leu Pro Asn
710 715 720

Cys Ile Glu Asp Pro Val Ser Pro Ile Val Leu Arg Leu Asn Phe
725 730 735

Ser Leu Val Gly Thr Pro Leu Ser Ala Phe Gly Asn Leu Arg Pro
740 745 750

Val Leu Ala Glu Asp Ala Gln Arg Leu Phe Thr Ala Leu Phe Pro
755 760 765

Phe Glu Lys Asn Cys Gly Asn Asp Asn Ile Cys Gln Asp Asp Leu
770 775 780

Ser Ile Thr Phe Ser Phe Met Ser Leu Asp Cys Leu Val Val Gly
785 790 795

Gly Pro Arg Glu Ser Asn Val Thr Val Thr Val Arg Asn Asp Gly
800 805 810

Glu Asp Ser Tyr Arg Thr Gln Val Thr Phe Phe Phe Pro Leu Asp
815 820 825

Leu Ser Tyr Arg Lys Val Ser Thr Leu Gln Asn Gln Arg Ser Gln
830 835 840

Arg Ser Trp Arg Leu Ala Cys Glu Ser Ala Ser Ser Thr Glu Val
845 850 855

Ser Gly Ala Leu Lys Ser Thr Ser Cys Ser Ile Asn His Pro Ile
860 865 870

Phe Pro Glu Asn Ser Glu Val Thr Phe Asn Ile Thr Phe Asp Val
875 880 885

Asp Ser Lys Ala Ser Leu Gly Asn Lys Leu Leu Leu Lys Ala Asn
890 895 900

Val Thr Ser Glu Asn Asn Met Pro Arg Thr Asn Lys Thr Glu Phe
905 910 915

Gln Leu Glu Leu Pro Val Lys Tyr Ala Val Tyr Met Val Val Thr
920 925 930

Ser His Gly Val Ser Thr Lys Tyr Leu Asn Phe Thr Ala Ser Glu
935 940 945

Asn Thr Ser Arg Val Met Gln His Gln Tyr Gln Val Ser Asn Leu
950 955 960

Gly Gln Arg Ser Pro Pro Ile Ser Leu Val Phe Leu Val Pro Val
965 970 975

Arg Leu Asn Gln Thr Val Ile Trp Asp Arg Pro Gln Val Thr Phe
980 985 990

Ser Glu Asn Leu Ser Ser Thr Cys His Thr Lys Glu Arg Leu Pro
995 1000 1005

Ser His Ser Asp Phe Leu Ala Glu Leu Arg Lys Ala Pro Val Val
1010 1015 1020

Asn Cys Ser Ile Ala Val Cys Gln Arg Ile Gln Cys Asp Ile Pro
1025 1030 1035

Phe Phe Gly Ile Gln Glu Glu Phe Asn Ala Thr Leu Lys Gly Asn
1040 1045 1050

Leu Ser Phe Asp Trp Tyr Ile Lys Thr Ser His Asn His Leu Leu
1055 1060 1065

Ile Val Ser Thr Ala Glu Ile Leu Phe Asn Asp Ser Val Phe Thr
1070 1075 1080

Leu Leu Pro Gly Gln Gly Ala Phe Val Arg Ser Gln Thr Glu Thr
1085 1090 1095

Lys Val Glu Pro Phe Glu Val Pro Asn Pro Leu Pro Leu Ile Val
1100 1105 1110

Gly Ser Ser Val Gly Gly Leu Leu Leu Leu Ala Leu Ile Thr Ala
1115 1120 1125

Ala Leu Tyr Lys Leu Gly Phe Phe Lys Arg Gln Tyr Lys Asp Met
1130 1135 1140

Met Ser Glu Gly Gly Pro Pro Gly Ala Glu Pro Gln
1145 1150

(2) INFORMATION FOR SEQ ID NO: 44:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 1163
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 44:

Met Thr Arg Thr Arg Ala Ala Leu Leu Leu Phe Thr Ala Leu Ala
5 10 15

Thr Ser Leu Gly Phe Asn Leu Asp Thr Glu Glu Leu Thr Ala Phe

20 25 30

Arg Val Asp Ser Ala Gly Phe Gly Asp Ser Val Val Gln Tyr Ala
35 40 50

Asn Ser Trp Val Val Val Gly Ala Pro Gln Lys Ile Thr Ala Ala
55 60 65

Asn Gln Thr Gly Gly Leu Tyr Gln Cys Gly Tyr Ser Thr Gly Ala
70 75 80

Cys Glu Pro Ile Gly Leu Gln Val Pro Pro Glu Ala Val Asn Met
85 90 95

Ser Leu Gly Leu Ser Leu Ala Ser Thr Thr Ser Pro Ser Gln Leu
100 105 115

Leu Ala Cys Gly Pro Thr Val His His Glu Cys Gly Arg Asn Met
120 125 130

Tyr Leu Thr Gly Leu Cys Phe Leu Leu Gly Pro Thr Gln Leu Thr
135 140 145

Gln Arg Leu Pro Val Ser Arg Gln Glu Cys Pro Arg Gln Glu Gln
150 155 160

Asp Ile Val Phe Leu Ile Asp Gly Ser Gly Ser Ile Ser Ser Arg
165 170 175

Asn Phe Ala Thr Met Met Asn Phe Val Arg Ala Val Ile Ser Gln
180 185 190

Phe Gln Arg Pro Ser Thr Gln Phe Ser Leu Met Gln Phe Ser Asn
195 200 205

Lys Phe Gln Thr His Phe Thr Phe Glu Glu Phe Arg Arg Thr Ser
215 220 225

Asn Pro Leu Ser Leu Leu Ala Ser Val His Gln Leu Gln Gly Phe
230 235 240

Thr Tyr Thr Ala Thr Ala Ile Gln Asn Val Val His Arg Leu Phe
245 250 255

His Ala Ser Tyr Gly Ala Arg Arg Asp Ala Thr Lys Ile Leu Ile
260 265 270

Val Ile Thr Asp Gly Lys Lys Glu Gly Asp Ser Leu Asp Tyr Lys
275 280 285

Asp Val Ile Pro Met Ala Asp Ala Ala Gly Ile Ile Arg Tyr Ala
290 295 300

Ile Gly Val Gly Leu Ala Phe Gln Asn Arg Asn Ser Trp Lys Glu
305 310 315

Leu Asn Asp Ile Ala Ser Lys Pro Ser Gln Glu His Ile Phe Lys
320 325 330

Val Glu Asp Phe Asp Ala Leu Lys Asp Ile Gln Asn Gln Leu Lys
335 340 345

Glu Lys Ile Phe Ala Ile Glu Gly Thr Glu Thr Thr Ser Ser Ser
350 355 360

Ser Phe Glu Leu Glu Met Ala Gln Glu Gly Phe Ser Ala Val Phe
365 370 375

Thr Pro Asp Gly Pro Val Leu Gly Ala Val Gly Ser Phe Thr Trp
380 385 390

Ser Gly Gly Ala Phe Leu Tyr Pro Pro Asn Met Ser Pro Thr Phe
395 400 405

Ile Asn Met Ser Gln Glu Asn Val Asp Met Arg Asp Ser Tyr Leu
415 420 425

Gly Tyr Ser Thr Glu Leu Ala Leu Trp Lys Gly Val Gln Ser Leu
430 435 440

Val Leu Gly Ala Pro Arg Tyr Gln His Thr Gly Lys Ala Val Ile
445 450 455

Phe Thr Gln Val Ser Arg Gln Trp Arg Met Lys Ala Glu Val Thr
460 465 470

Gly Thr Gln Ile Gly Ser Tyr Phe Gly Ala Ser Leu Cys Ser Val
475 480 485

Asp Val Asp Thr Asp Gly Ser Thr Asp Leu Val Leu Ile Gly Ala
490 495 500

Pro His Tyr Tyr Glu Gln Thr Arg Gly Gly Gln Val Ser Val Cys
505 510 515

Pro Leu Pro Arg Gly Trp Arg Arg Trp Trp Cys Asp Ala Val Leu
520 525 530

Tyr Gly Glu Gln Gly His Pro Trp Gly Arg Phe Gly Ala Ala Leu
535 540 545

Thr Val Leu Gly Asp Val Asn Gly Asp Lys Leu Thr Asp Val Val
550 555 560

Ile Gly Ala Pro Gly Glu Glu Glu Asn Arg Gly Ala Val Tyr Leu
565 570 575

Phe His Gly Val Leu Gly Pro Ser Ile Ser Pro Ser His Ser Gln
580 585 590

Arg Ile Ala Gly Ser Gln Leu Ser Ser Arg Leu Gln Tyr Phe Gly
595 600 605

Gln Ala Leu Ser Gly Gly Gln Asp Leu Thr Gln Asp Gly Leu Val
610 615 620

Asp Leu Ala Val Gly Ala Arg Gly Gln Val Leu Leu Leu Arg Thr
625 630 635

Arg Pro Val Leu Trp Val Gly Val Ser Met Gln Phe Ile Pro Ala
640 645 650

Glu Ile Pro Arg Ser Ala Phe Glu Cys Arg Glu Gln Val Val Ser
655 670 675

Glu Gln Thr Leu Val Gln Ser Asn Ile Cys Leu Tyr Ile Asp Lys
680 685 690

Arg Ser Lys Asn Leu Leu Gly Ser Arg Asp Leu Gln Ser Ser Val
695 670 675

Thr Leu Asp Leu Ala Leu Asp Pro Gly Arg Leu Ser Pro Arg Ala
680 685 690

Thr Phe Gln Glu Thr Lys Asn Arg Ser Leu Ser Arg Val Arg Val
695 700 705

Leu Gly Leu Lys Ala His Cys Glu Asn Phe Asn Leu Leu Leu Pro
710 715 720

Ser Cys Val Glu Asp Ser Val Thr Pro Ile Thr Leu Arg Leu Asn
725 730 735

Phe Thr Leu Val Gly Lys Pro Leu Leu Ala Phe Arg Asn Leu Arg
740 745 750

Pro Met Leu Ala Ala Leu Ala Gln Arg Tyr Phe Thr Ala Ser Leu
755 760 765

Pro Phe Glu Lys Asn Cys Gly Ala Asp His Ile Cys Gln Asp Asn
770 775 780

Leu Gly Ile Ser Phe Ser Phe Pro Gly Leu Lys Ser Leu Leu Val
785 790 795

Gly Ser Asn Leu Glu Leu Asn Ala Glu Val Met Val Trp Asn Asp
800 805 810

Gly Glu Asp Ser Tyr Gly Thr Thr Ile Thr Phe Ser His Pro Ala

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                815                 820                 825

Gly Leu Ser Tyr Arg Tyr Val Ala Glu Gly Gln Lys Gln Gly Gln
                830                 835                 840

Leu Arg Ser Leu His Leu Thr Cys Asp Ser Ala Pro Val Gly Ser
                845                 850                 855

Gln Gly Thr Trp Ser Thr Ser Cys Arg Ile Asn His Leu Ile Phe
                860                 865                 870

Arg Gly Gly Ala Gln Ile Thr Phe Leu Ala Thr Phe Asp Val Ser
                875                 880                 885

Pro Lys Ala Val Leu Gly Asp Arg Leu Leu Leu Thr Ala Asn Val
                890                 895                 900

Ser Ser Glu Asn Asn Thr Pro Arg Thr Ser Lys Thr Thr Phe Gln
                905                 910                 915

Leu Glu Leu Pro Val Lys Tyr Ala Val Tyr Thr Val Val Ser Ser
                920                 925                 930

His Glu Gln Phe Thr Lys Tyr Leu Asn Phe Ser Glu Ser Glu Glu
                935                 940                 945

Lys Glu Ser His Val Ala Met His Arg Tyr Gln Val Asn Asn Leu
                950                 955                 960

Gly Gln Arg Asp Leu Pro Val Ser Ile Asn Phe Trp Val Pro Val
                965                 970                 975

Glu Leu Asn Gln Glu Ala Val Trp Met Asp Val Glu Val Ser His
                980                 985                 990

Pro Gln Asn Pro Ser Leu Arg Cys Ser Ser Glu Lys Ile Ala Pro
                995                 1000                1005

Pro Ala Ser Asp Phe Leu Ala His Ile Gln Lys Asn Pro Val Leu
                1010                1015                1020

Asp Cys Ser Ile Ala Gly Cys Leu Arg Phe Arg Cys Asp Val Pro
                1025                1030                1035

Ser Phe Ser Val Gln Glu Glu Leu Asp Phe Thr Leu Lys Gly Asn
                1040                1045                1050

Leu Ser Phe Gly Trp Val Arg Gln Ile Leu Gln Lys Lys Val Ser
                1055                1060                1065

Val Val Ser Val Ala Glu Ile Thr Phe Asp Thr Ser Val Tyr Ser
                1070                1075                1080
```

Gln Leu Pro Gly Gln Glu Ala Phe Met Arg Ala Gln Thr Thr Thr
1085 1090 1095

Val Leu Glu Lys Tyr Lys Val His Asn Pro Thr Pro Leu Ile Val
1100 1105 1110

Gly Ser Ser Ile Gly Gly Leu Leu Leu Ala Leu Ile Thr Ala
1115 1120 1125

Val Leu Tyr Lys Val Gly Phe Phe Lys Arg Gln Tyr Lys Glu Met
1130 1135 1140

Met Glu Glu Ala Asn Gly Gln Ile Ala Pro Glu Asn Gly Thr Gln
1145 1150 1155

Thr Pro Ser Pro Pro Ser Glu Lys
1160

(2) INFORMATION FOR SEQ ID NO: 45:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 769
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 45:

Met Leu Gly Leu Arg Pro Pro Leu Leu Ala Leu Val Gly Leu Leu
5 10 15

Ser Leu Gly Cys Val Leu Ser Gln Glu Cys Thr Lys Phe Lys Val
20 25 30

Ser Ser Cys Arg Glu Cys Ile Glu Ser Gly Pro Gly Cys Thr Trp
35 40 50

Cys Gln Lys Leu Asn Phe Thr Gly Pro Gly Asp Pro Asp Ser Ile
55 60 65

Arg Cys Asp Thr Arg Pro Gln Leu Leu Met Arg Gly Cys Ala Ala
70 75 80

Asp Asp Ile Met Asp Pro Thr Ser Leu Ala Glu Thr Gln Glu Asp
85 90 95

His Asn Gly Gly Gln Lys Gln Leu Ser Pro Gln Lys Val Thr Leu
100 105 115

Tyr Leu Arg Pro Gly Gln Ala Ala Ala Phe Asn Val Thr Phe Arg

120 125 130

Arg Ala Lys Gly Tyr Pro Ile Asp Leu Tyr Tyr Leu Met Asp Leu
135 140 145

Ser Tyr Ser Met Leu Asp Asp Leu Arg Asn Val Lys Lys Leu Gly
150 155 160

Gly Asp Leu Leu Arg Ala Leu Asn Glu Ile Thr Glu Ser Gly Arg
165 170 175

Ile Gly Phe Gly Ser Phe Val Asp Lys Thr Val Leu Pro Phe Val
180 185 190

Asn Thr His Pro Asp Lys Leu Arg Asn Pro Cys Pro Asn Lys Glu
195 200 205

Lys Glu Cys Gln Pro Pro Phe Ala Phe Arg His Val Leu Lys Leu
215 220 225

Thr Asn Asn Ser Asn Gln Phe Gln Thr Glu Val Gly Lys Gln Leu
230 235 240

Ile Ser Gly Asn Leu Asp Ala Pro Glu Gly Gly Leu Asp Ala Met
245 250 255

Met Gln Val Ala Ala Cys Pro Glu Glu Ile Gly Trp Arg Asn Val
260 265 270

Thr Arg Leu Leu Val Phe Ala Thr Asp Asp Gly Phe His Phe Ala
275 280 285

Gly Asp Gly Lys Leu Gly Ala Ile Leu Thr Pro Asn Asp Gly Arg
290 295 300

Cys His Leu Glu Asp Asn Leu Tyr Lys Arg Ser Asn Glu Phe Asp
305 310 315

Tyr Pro Ser Val Gly Gln Leu Ala His Lys Leu Ala Glu Asn Asn
320 325 330

Ile Gln Pro Ile Phe Ala Val Thr Ser Arg Met Val Lys Thr Tyr
335 340 345

Glu Lys Leu Thr Glu Ile Ile Pro Lys Ser Ala Val Gly Glu Leu
350 355 360

Ser Glu Asp Ser Ser Asn Val Val His Leu Ile Lys Asn Ala Tyr
365 370 375

Asn Lys Leu Ser Ser Arg Val Phe Leu Asp His Asn Ala Leu Pro
380 385 390

Asp Thr Leu Lys Val Thr Tyr Asp Ser Phe Cys Ser Asn Gly Val
395 400 405

Thr His Arg Asn Gln Pro Arg Gly Asp Cys Asp Gly Val Gln Ile
415 420 425

Asn Val Pro Ile Thr Phe Gln Val Lys Val Thr Ala Thr Glu Cys
430 435 440

Ile Gln Glu Gln Ser Phe Val Ile Arg Ala Leu Gly Phe Thr Asp
445 450 455

Ile Val Thr Val Gln Val Leu Pro Gln Cys Glu Cys Arg Cys Arg
460 465 470

Asp Gln Ser Arg Asp Arg Ser Leu Cys His Gly Lys Gly Phe Leu
475 480 485

Glu Cys Gly Ile Cys Arg Cys Asp Thr Gly Tyr Ile Gly Lys Asn
490 495 500

Cys Glu Cys Gln Thr Gln Gly Arg Ser Ser Gln Glu Leu Glu Gly
505 510 515

Ser Cys Arg Lys Asp Asn Asn Ser Ile Ile Cys Ser Gly Leu Gly
520 525 530

Asp Cys Val Cys Gly Gln Cys Leu Cys His Thr Ser Asp Val Pro
535 540 545

Gly Lys Leu Ile Tyr Gly Gln Tyr Cys Glu Cys Asp Thr Ile Asn
550 555 560

Cys Glu Arg Tyr Asn Gly Gln Val Cys Gly Gly Pro Gly Arg Gly
565 570 575

Leu Cys Phe Cys Gly Lys Cys Arg Cys His Pro Gly Phe Glu Gly
580 585 590

Ser Ala Cys Gln Cys Glu Arg Thr Thr Glu Gly Cys Leu Asn Pro
595 600 605

Arg Arg Val Glu Cys Ser Gly Arg Gly Arg Cys Arg Cys Asn Val
610 615 620

Cys Glu Cys His Ser Gly Tyr Gln Leu Pro Leu Cys Gln Glu Cys
625 630 635

Pro Gly Cys Pro Ser Pro Cys Gly Lys Tyr Ile Ser Cys Ala Glu
640 645 650

Cys Leu Lys Phe Glu Lys Gly Pro Phe Gly Lys Asn Cys Ser Ala
655 670 675

Ala Cys Pro Gly Leu Gln Leu Ser Asn Asn Pro Val Lys Gly Arg
680 685 690

Thr Cys Lys Glu Arg Asp Ser Glu Gly Cys Trp Val Ala Tyr Thr
695 670 675

Leu Glu Gln Gln Asp Gly Met Asp Arg Tyr Leu Ile Tyr Val Asp
680 685 690

Glu Ser Arg Glu Cys Val Ala Gly Pro Asn Ile Ala Ala Ile Val
695 700 705

Gly Gly Thr Val Ala Gly Ile Val Leu Ile Gly Ile Leu Leu Leu
710 715 720

Val Ile Trp Lys Ala Leu Ile His Leu Ser Asp Leu Arg Glu Tyr
725 730 735

Arg Arg Phe Glu Lys Glu Lys Leu Lys Ser Gln Trp Asn Asn Asp
740 745 750

Asn Pro Leu Phe Lys Ser Ala Thr Thr Thr Val Met Asn Pro Lys
755 760 765

Phe Ala Glu Ser

(2) INFORMATION FOR SEQ ID NO: 46:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 46:

Asp Val Asp Ser Asn Gly Ser Thr Asp
5

(2) INFORMATION FOR SEQ ID NO: 47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 47:

Asp Val Asn Gly Asp Lys Leu Thr Asp
5

(2) INFORMATION FOR SEQ ID NO: 48:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 48:

Asp Leu Thr Met Asp Gly Leu Val Asp
5

(2) INFORMATION FOR SEQ ID NO: 49:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 9
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 49:

Asp Ser Asp Met Asn Asp Ala Tyr Leu
5

(2) INFORMATION FOR SEQ ID NO: 50:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 33
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 50:

Asn Ala Phe Lys Ile Leu Val Val Ile Thr Asp Gly Glu Lys Phe
5 10 15

Gly Asp Pro Leu Gly Tyr Glu Asp Val Ile Pro Glu Ala Asp Arg
20 25 30

Glu Gly Val

(2) INFORMATION FOR SEQ ID NO: 51:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 5
(B) TYPE: amino acid
(D) TOPOLOGY: linear

(ii) SEQUENCE DESCRIPTION: SEQ ID NO: 51:

Asp Gly Glu Lys Phe
5

Claims

1. A purified peptide comprising at least one extracellular region of a β2 integrin subunit capable of inhibiting a CD11/CD18 mediated immune response, said peptide lacking the transmembrane and cytoplasmic portions of said β2 integrin subunit, wherein said subunit is CD11b, CD11c or CD18.

2. The purified peptide of claim 1 wherein said β2 integrin subunit is CD11b.

3. The peptide of claim 3, said peptide comprising all or part of the A domain of CD11b.

4. The peptide of claim 3, said peptide comprising one of the following amino acid sequences:
   a. DIAFLIDGS (SEQ ID NO: 32),
   b. FRRMKEFVS (SEQ ID NO: 33),
   c. FKILVVITDGE (SEQ ID NO: 34),
   d. VIRYVIGVGDA (SEQ ID NO: 35),

5. The peptide of claim 3, said peptide comprising one of the following amino acid sequences:
   a. DGEKFGDPLG (SEQ ID NO: 36),
   b. YEDVIPEADR (SEQ ID NO: 37),
   c. DGEKFGDPLGYEDVIPEADR (SEQ ID NO: 17) or
   d. NAFKILVVITDGEKFGDPLGYEDVIPEADREGV (SEQ ID NO:50)
   e. DGEKF (SEQ ID NO: 51)

6. The peptide of claim 2 wherein said peptide comprises the following amino acid sequence: YYEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 38).

7. The peptide of claim 2 wherein said peptide comprises the following amino acid sequence: KSTRDRLR (SEQ ID NO: 15).

8. The peptide of claim 2, said peptide comprising one of the following amino acid sequences:

a. AYFGASLCSVDVDSNGSTDLVLIGAP (SEQ ID NO: 1),
b. GRFGAALTVLGDVNGDKLTDVAIGAP (SEQ ID NO: 2),
c. QYFGQSLSGGQDLTMDGLVDLTVGAQ (SEQ ID NO: 3),
d. YEQTRGGQVSVCPLPRGRARWQCDAV (SEQ ID NO: 4),
e. DIAFLIDGSGSIIPHDFRRMK (SEQ ID NO: 5),
f. RRMKEFVSTVMEQLKKSKTLF (SEQ ID NO: 6),
g. SLMQYSEEFRIHFTFKEFQNN (SEQ ID NO: 7),
h. PNPRSLVKPITQLLGRTHTATGIRK (SEQ ID NO: 8),
i. RKVVRELFNITNGARKNAFK (SEQ ID NO: 9),
j. FKILVVITDGEKFGDPLGYEDVIPEADR (SEQ ID NO: 10),
k. REGVIRYVIGVGDAFRSEKSR (SEQ ID NO: 11),
l. QELNTIASKPPRDHVFQVNNFE (SEQ ID NO: 12),
m. ALKTIQNQLREKIFAIEGT (SEQ ID NO: 13),
n. QTGSSSSFEHEMSQE (SEQ ID NO: 14),
o. FRSEKSRQELNTIASKPPRDHV (SEQ ID NO: 16),
p. KEFQNNPNPRSL (SEQ ID NO: 18),
q. GTQTGSSSSFEHEMSQEG (SEQ ID NO: 19),
r. SNLRQQPQKFPEALRGCPQEDSD (SEQ ID NO: 20),
s. RQNTGMWESNANVKGT (SEQ ID NO: 21),
t. TSGSGISPSHSQRIA (SEQ ID NO: 22),
u. NQRGSLYQCDYSTGSCEPIR (SEQ ID NO: 23),
v. PRGRARWQC (SEQ ID NO: 24),
w. KLSPRLQYFGQSLSGGQDLT (SEQ ID NO: 25),
x. QKSTRDRLREGQ (SEQ ID NO: 26),
y. SGRPHSRAVFNETKNSTRRQTQ (SEQ ID NO: 27),
z. CETLKLQLPNCIEDPV (SEQ ID NO: 28),
a'. FEKNCGNDNICQDDL (SEQ ID NO: 29),
b'. VRNDGEDSYRTQ (SEQ ID NO: 30),
c'. SYRKVSTLQNQRSQRS (SEQ ID NO: 31).

9. The peptide of claim 2, said peptide comprising one or more metal binding domains of CD11b.

10. The peptide of claim 9, said metal binding domains encompassing amino acids 358-412, 426-483, 487-553, and 554-614 of CD11b.

11. The peptide of claim 10, said peptide comprising one of the following sequences:
a. DVDSNGSTD (SEQ ID NO: 46),
b. DVNGDKLTD (SEQ ID NO: 47),
c. DLTMDGLVD (SEQ ID NO: 48), or
d. DSDMNDAYL (SEQ ID NO: 49)

12. The peptide of claim 1 or 2 wherein said peptide is soluble under physiological conditions.

13. A heterodimer comprising a first peptide and a second peptide, said first peptide comprising at least one extracellular region of a CD11 subunit and lacking the transmembrane and cytoplasmic portions of said CD11 subunit, said second peptide comprising at least one extracellular region of CD18 and lacking the transmembrane and cytoplasmic portions of CD18, said peptides being associated to form said heterodimer, said heterodimer being capable of inhibiting a CD11/CD18 mediated immune response.

14. The heterodimer of claim 13 wherein said CD11 subunit is CD11b.

15. The heterodimer of claim 13 wherein said CD11 subunit is CD11c.

16. The heterodimer of claim 14 wherein said heterodimer

is $CD11b^{1089}/CD18^{699}$

17. A method of controlling phagocyte-mediated tissue damage to a human patient, said method comprising administering a therapeutic composition to a patient said therapeutic composition comprising a physiologically acceptable carrier and either a peptide according to claim 1 or 2 or a heterodimer according to claim 13.

18. The method of claim 17 wherein said therapeutic composition is administered to control phagocyte-mediated tissue damage associated with ischemia-reperfussion.

19. The method of claim 17 wherein said therapeutic composition is administered to control phagocyte-mediated tissue damage to the heart muscle associated with reduced perfusion of heart tissue during acute cardiac insufficiency.

20. A method of producing a recombinant β2 integrin heterodimer, said method comprising:

(a) providing a recombinant cell encoding a CD11 peptide lacking both the transmembrane domain and the cytoplasmic domain and a CD18 peptide lacking both the transmembrane domain and the cytoplasmic domain;

(b) culturing said recombinant cell; and

(c) isolating said heterodimer from the culture supernatant.

21. The method of claim 20 wherein said recombinant β2 integrin heterodimer is soluble under physiological conditions.

22. The method of claim 20 wherein said CD11 peptide is a CD11b peptide.

23. The method of claim 20 wherein said soluble CD11 peptide is a recombinant CD11c peptide.

24. A monoclonal antibody which is raised to the peptide of claim 1 or claim 2 or the heterodimer of claim 13, said monoclonal antibody being capable of inhibiting a CD11/CD18 mediated immune response.

FIGURE 1

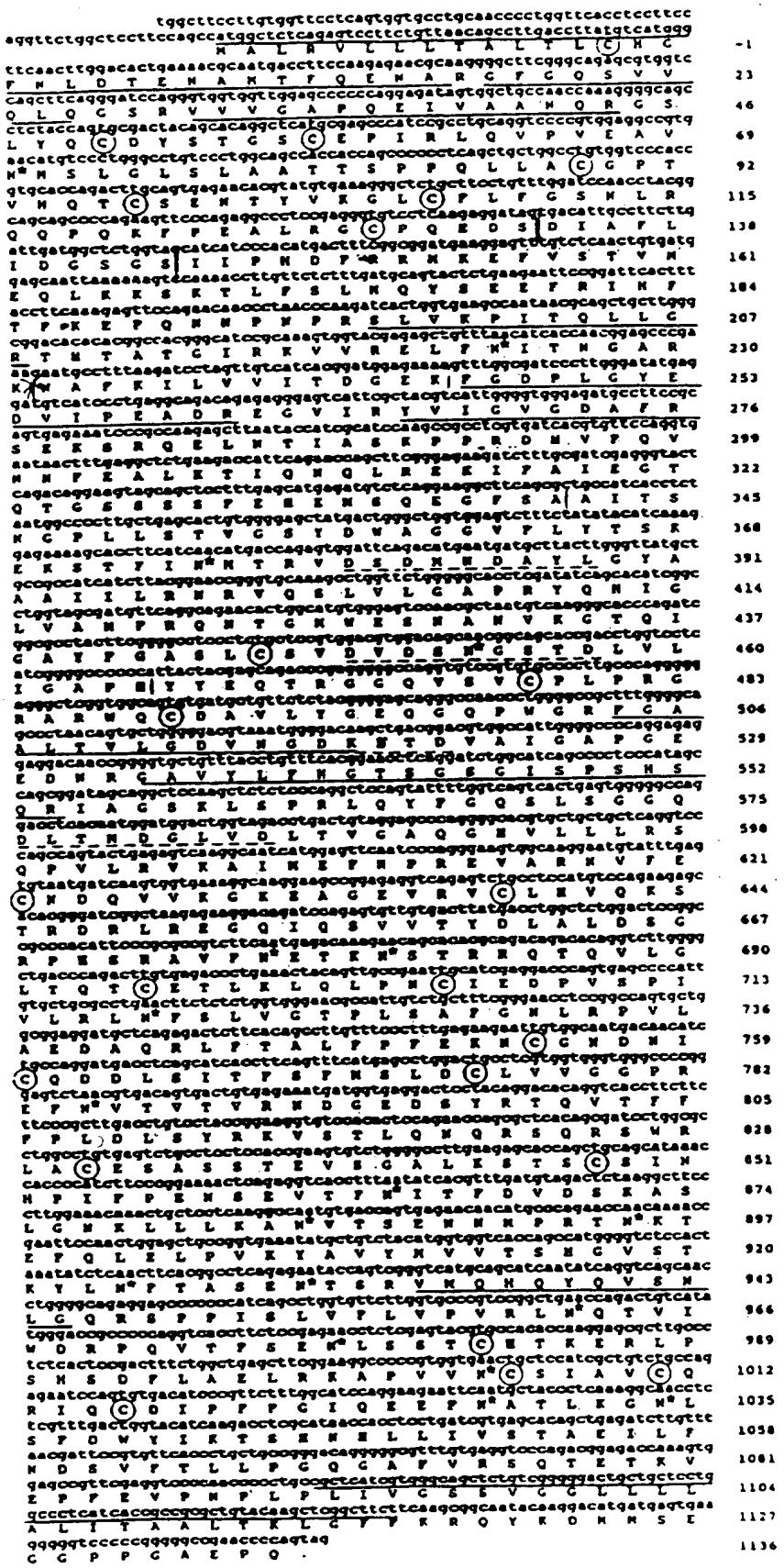

FIGURE 2

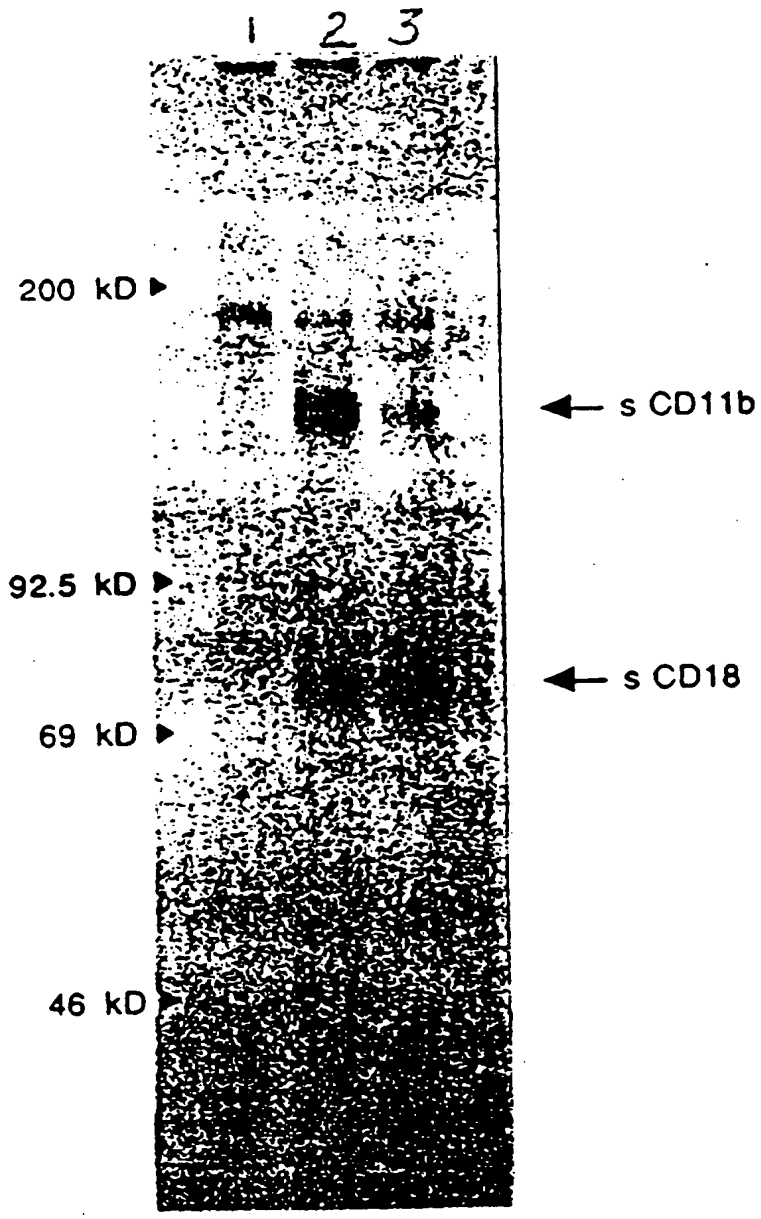

FIGURE 3

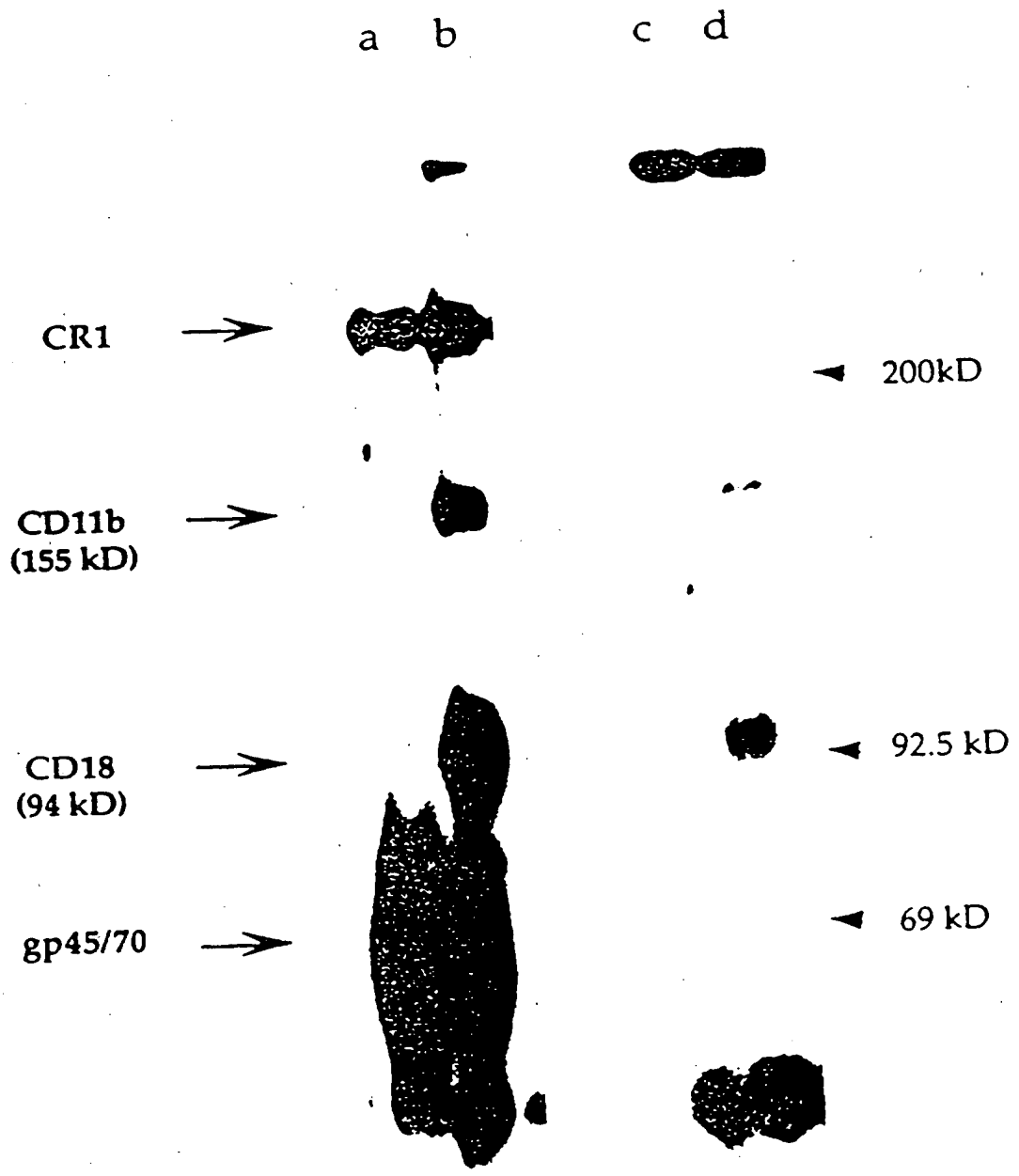

FIGURE 4

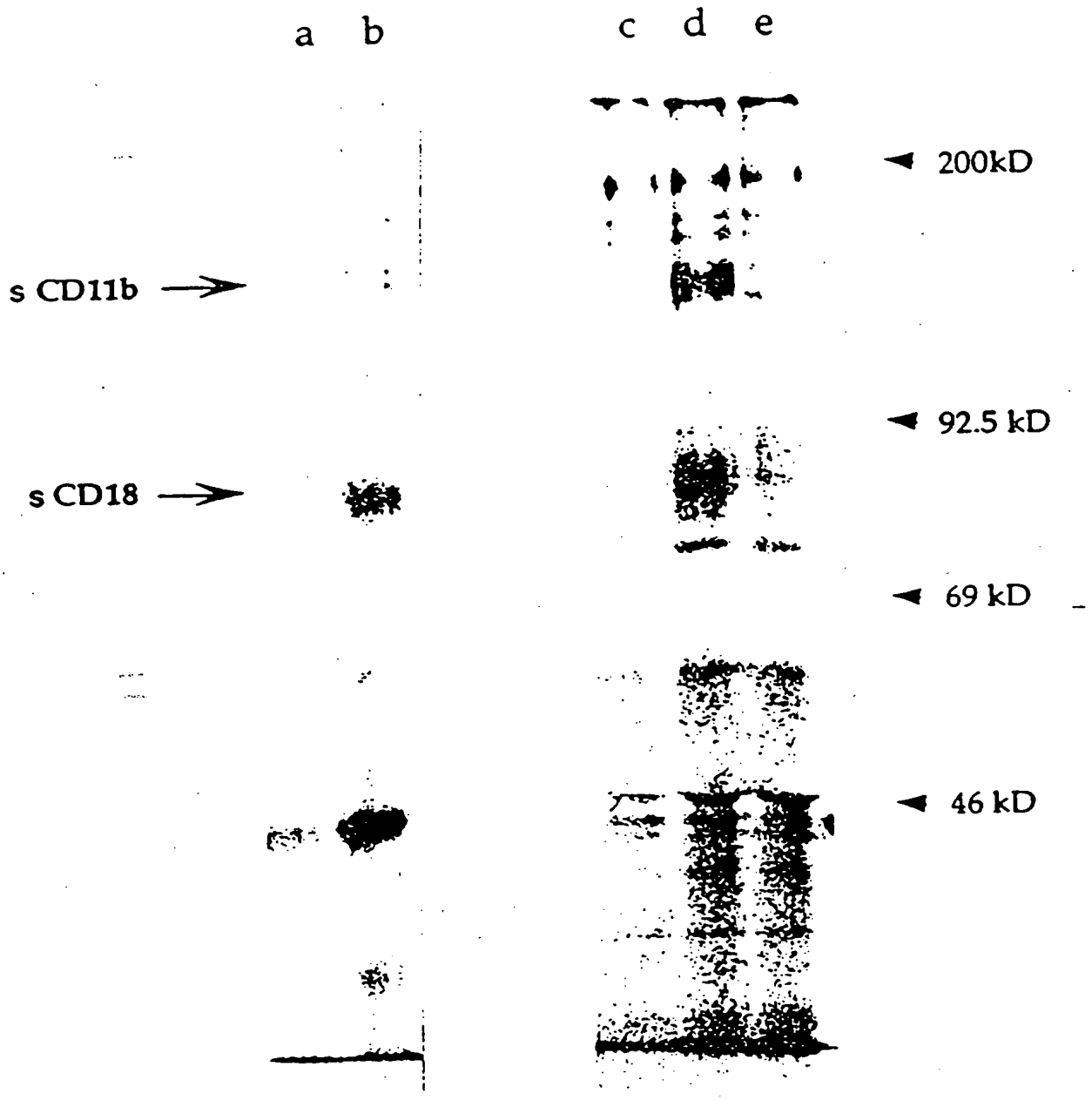

FIGURE 5

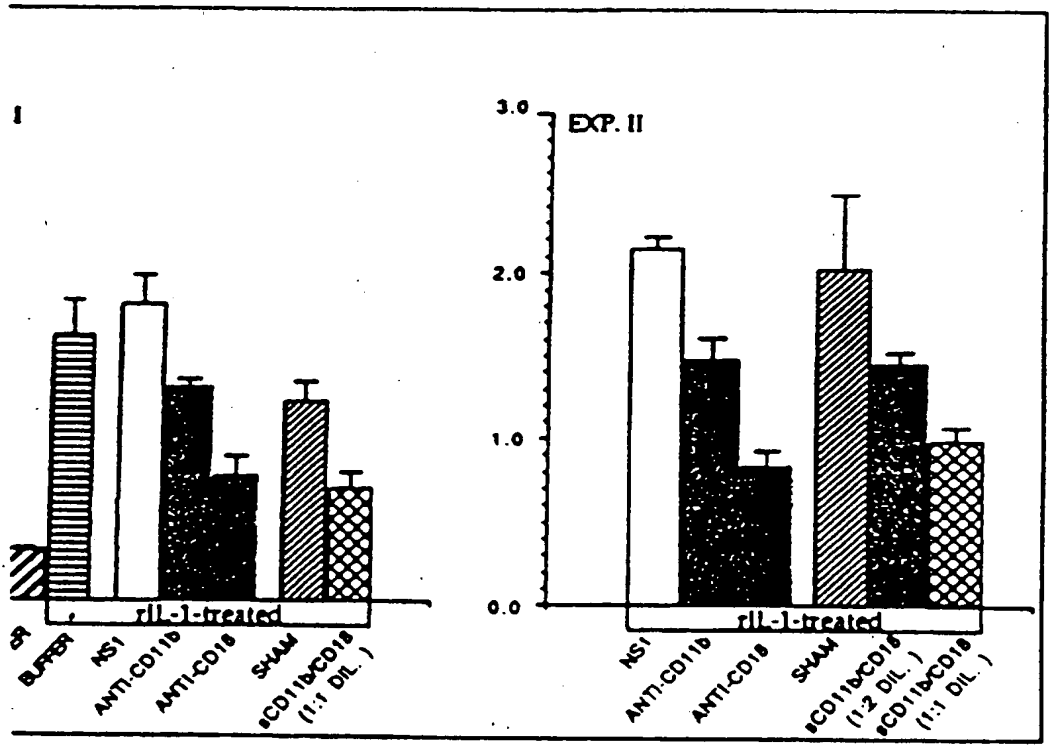
I
rIL-1-treated
BUFFER
NS1
ANTI-CD11b
ANTI-CD18
SHAM
sCD11b/CD18 (1:1 DIL.)
EXP. II
3.0
2.0
1.0
0.0
rIL-1-treated
NS1
ANTI-CD11b
ANTI-CD18
SHAM
sCD11b/CD18 (1:2 DIL.)
sCD11b/CD18 (1:1 DIL.)

FIGURE 8

INTERNATIONAL SEARCH REPORT

International Application No PCT/US91/04338

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

IPC(5): A61K 37/02, 39/00; C07K 7/06, 7/10, 13/00, 15/28, 7/08

U.S.: 530/324,325,326,327,328,350,387; 514/12,13,14,15

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System [5]	Classification Symbols
US	530/324,325,326,327,328,350,387; 514/12,13,14,15

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [6]

Automated Patent Search, Chemical Abstract Service

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category * [15]	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
Y	Cell, Vol. 48, issued 27 February 1987, Kishimoto et al. "Cloning of the B Subunit of the Leukocyte Adhesion Proteins: Homology to an Extracellular Matrix Receptor Defines a Novel Super-gene Family" pp.681-690, see Fig. 2 including legend.	1-23
Y	The EMBO Journal, vol. 7, No. 5, issued May 1988, Pytela, "Amino acid sequence of the Murine Mac-1 chair reveals homology with the integrin family and an additional domain related to Von Willebrand factor" pp. 1371-1378, see Fig. 2.	1-23

* Special categories of cited documents: [19]

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]

08 August 1991

Date of Mailing of this International Search Report [2]

20 SEP 1991

International Searching Authority [1]

ISA/US

Signature of Authorized Officer [20]

Nina Ossanna, Ph.D.

Form PCT/ISA/210 (second sheet) (May 1986)

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, ** with indication, where appropriate, of the relevant passages **	Relevant to Claim No **
Y	The Journal of Biological Chemistry, vol. 263, No. 25, issued 05 September 1988, Corbi et al. "The Human Leukocyte Adhesion Glycoprotein Mac-1 (Complement Receptor Type 3, CD11b) Subunit" pp. 12403-12411. See Figs. 2 & 7.	1-23
X Y	The Journal of Immunology, vol. 137, No. 10, issued 15 November 1986, Dana et al. "Two Functional Domains in the Phagocyte Membrane Glycoprotein Mo1 Identified with Monoclonal Antibodies" pp. 3259-3263. See abstract.	24 1-23
Y	Proc. Natl. Acad. Sci. USA, vol. 83, issued September 1986, Mehra et al., "Efficient Mapping of Protein Antigenic Determinants" pp. 7013-7017. See entire article.	1-23